

Mrs Thatcher Comes Down from Sinai

THE Government's white paper on education policy (*Education: A Framework for Expansion*, HMSO, £0.315) may well make up by its scope for the difficulties that have been created in British universities by the procrastination over several months about an announcement of plans for the quinquennium which begins with the next academic year. For Mrs Margaret Thatcher, the Secretary of State for Education and Science, has now produced in a single document her proposals for allocating a substantially larger share of national resources to the several sectors of the educational system. As a whole, the plan is liberal and even imaginative. It is especially welcome that there are to be places in nursery schools for all children between three and five whose parents wish them to attend, that in-service training for teachers should be built into the system at the rate of one term of training for each seven years of teaching service and that the decline of the pressure of numbers on the primary and secondary schools should be used as an opportunity for a further improvement of the teacher-student ratio. Even those with a vested interest in higher education will recognize that these objectives are entirely worthy. Where the schools are concerned, the weaknesses of the white paper consist in its proposals on teacher training—essentially an issue in higher education—and the doubts that there must be that extra funds and extra teachers will not without structural change provide a commensurate improvement of performance. On higher education, the new proposals are less well-considered and, in particular, have nothing but platitudes to offer about the ambiguous relationship between universities and other institutions.

The past two decades have seen enormous upheavals in all sectors of British education, and a decade of consolidation will be valuable. The secondary schools have been most seriously affected, not merely by the raising of the school-leaving age to 16 (more than a quarter of a century after this was declared a national priority in the Education Act of 1944) but by the reorganization of many school systems along comprehensive lines. Those who read Mrs Thatcher's manifesto will be painfully aware of the defects of the system which has emerged. For there is often a serious gap between the promise and the performance of the comprehensive schools, many of which have been crudely cobbled together by administrative sleight of hand. Experience has shown what should have been anticipated—that the headmasters and headmistresses of comprehensive schools need to be different kinds of animals from the dominoes who ruled the old grammar schools, as much concerned with the social problems of their students and with the politics of education as with the techniques of formal instruction. But too many of the comprehensive schools still live uneasily in the academic shadows of old-fashioned selective schools, with the result that they are not supplied with students who would provide a natural stimulus for excellence. There is a danger that the comprehensive

schools—or at least a large proportion of them—will remain educational ghettos even if their frequently acute shortages of teachers are somehow remedied, which is why it would have been valuable if Mrs Thatcher had acknowledged that a problem of quality exists. Then she or her successors would have had an incentive to ask when, among other things, it will be time to trade a restriction of parental choice of the publicly supported schools which their children attend for a promise that comprehensive schools will be able to cater properly even for the academically inclined minority. This is unfashionable talk, but there is now a danger that the capacity of the secondary schools to do their best by all their students will be compromised by the natural wish of governments—even Conservative governments—and local authorities for a quiet life.

Mrs Thatcher's proposals on teacher training are similarly permissive. The colleges of education have grown three-fold since the early 1960s, and it has in the past few years been accepted as a matter of government policy that only those properly qualified as professional teachers (which is also possible at university institutes of education) will in future be allowed to teach in British schools. The difficulty is that this enlarged system has grown up in such a way that many of those who finish up as teachers in British schools are being required, under the present system, to make decisions about their long-term careers when they themselves leave school and not, as would be appropriate, after they have had some taste of higher education. The report of Mrs Thatcher's committee of inquiry into teacher training, with Lord James as chairman, may have said the right things about teacher training and related subjects, but it entirely dodged the question of whether it might not be far preferable that potential teachers should be recruited from among, say, young men and women aged nineteen in all sectors of higher education. It is true that such a policy would entail a weakening of the present links between local authorities and the colleges of education, and the formation instead of links with other institutions of higher education—the universities or polytechnics, for example—but, politics apart, such changes would in any case be valuable in themselves. And is it wise for Mrs Thatcher to commit herself even as tentatively as she does in this white paper to the principle that the teaching profession—which implies the teaching unions—should have a "major but not exclusive voice" in determining the criteria for professional qualifications in teaching?

The weakest parts of Mrs Thatcher's plan are, however, those concerned with higher education. She says, quite properly, that there must be a continuing growth of higher education, and the proportions of young men and women going on to higher education after school are expected to rise from 15 per cent in 1971 (a splendid improvement on the ratio of 7 per cent in 1961) to 22 per cent in 1981. This growth will imply an increase in the number of places in all kinds of institutions of



higher education (colleges of education included) from 463,000 in 1971 to 750,000 or thereabouts in 1981. So far, so good. The difficulty is that Mrs Thatcher has without much argument decided that the most rapid expansion will be in the polytechnics, but has done nothing to help bridge the gulf which threatens to separate these institutions from the universities or even to define what she considers the role of the universities should be. To be sure, the universities will continue to grow—the white paper estimates that the number of places in universities will increase in the decade to 1981 from 236,000 to 375,000, but there is to be a reduction in the proportions (though not necessarily in the absolute numbers) of those following postgraduate courses, while the white paper makes it plain that much of the growth in higher education as a whole will take place in those institutions which respond joyously to Mrs Thatcher's open exhortation for the institution of two-year courses. The trouble is, of course, that the concept of the two-year course (leading to yet another academic degree to be known as a Diploma of Higher Education) has not yet been tested even in the rudimentary sense of finding out what potential employers think about it. Without fuller discussion with all institutions, there is a danger that the future expansion of the higher education system will be driven by a kind of Gresham's law, with courses of higher education as yet untried growing at the expense of others.

The question overlooked in Mrs Thatcher's plan is the intended relationship between the universities and the other institutions of higher education. When Mr Anthony Crosland first embarked on the creation of polytechnics, he was much influenced by the cheapness of the old colleges of technology and by the general and dubious argument that Britain needed a "binary" system of higher education in which polytechnics would provide a less "academic" education than the universities. Experience has, however, shown that polytechnics are not that cheap—although they have the convenience (from the government's point of view) of being financed by local authorities—and there is every likelihood that their apparent economy will be further eroded when the student-staff ratio at the universities has been forced up to 10:1 (as is now intended). The result is, however, that the supposed virtues of the binary system conceal a state of affairs in which the polytechnics are the second choice for a large but unknown proportion of the students who attend them. And although some of these institutions are splendid places, others appear to be unsure whether they are intended to be vocational schools or simulations of old-fashioned universities. But if the objective is, as it should be, to provide all students in higher education with the instruction best suited to their needs, it would be much better if the government were to work for some common framework within which the universities and the polytechnics could flexibly co-exist, exchanging students and teachers and sharing common criteria of educational performance. Much of the public money to be spent on higher education in the decade ahead will be wasted if this nettle is not quickly grasped.

In the universities, the grants for the next five years, which have now been made public, will be a disappointment, although the intended growth of student numbers to 306,000 (full-time students) by 1976–77 is enough to keep up the momentum of recent years. It is, however,

more alarming that the recurrent grants now decided for the universities represent a reduction of 5 per cent in the cost of teaching each full-time university student (or his part-time equivalent). Plainly the universities will have to change their student-staff ratios, whether they like it or not. There will, moreover, be very little scope for innovation (which might in the long run be a source of economy). In all the circumstances, it is to be hoped that the University Grants Committee will be given (by the universities as well as the government) freedom to work for the kinds of rationalization within the university system that have for too long been necessary. The universities themselves, still supposedly autonomous, should urgently look for ways of making themselves less immediately susceptible to what are in effect government directives—on questions, for example, such as the admissibility of undergraduate courses lasting for four years. Alternative sources of finance, however small, will be more than worth their weight in gold in the years ahead.

Making Amends

ONE of the most immediate consequences of the announcement, last July, of the British Government's plans for the reorganization of civil research was that the House of Commons Select Committee on Science and Technology lapsed into an injured sulk. And it is true that it would have been courteous, to say the least of it, if the government had done more to acknowledge that the committee had worked hard, if misguidedly, to produce four detailed reports on the organization of publicly supported research—the announcement did no more than brush aside the committee's familiar theme that all will be well once there is a Minister for Research and Development. Now, after a not indecent interval, the government has made amends, and the government itself (which is in this case a pseudonym for Lord Jellicoe, the Lord Privy Seal) and the Department of Trade and Industry have published closely reasoned arguments for not doing what the Select Committee wanted (see page 373). The riposte to the Select Committee, as it turns out, is a good deal more interesting than it might have been, and is a useful gloss on the declaration of policy already made.

First, the Department of Trade and Industry has provided a fuller explanation of how its requirements boards will function than any which it has been possible to glean by reading between the lines of previously published documents. The requirements boards (of which there are to be six) will, it seems, now have responsibility for commissioning research at the department's own laboratories as well as non-nuclear work at the laboratories of the Atomic Energy Authority and work of all kinds which is at present put out to industrial laboratories, universities and the research councils. If the Department of Trade and Industry is to be taken at its word, the requirements boards will between them determine not merely the balance of the department's expenditure on research and development but also the way in which it is carried out. Certainly it will help to make the evolution of policy apparent and it is rational that the boards are required to produce an annual report. One snag

is that the department will not submit to the boards for discussion and decision proposals to spend money on research and development in industry, where "the primary objective is to provide direct assistance to industry", which implies that schemes like that under which International Computers Limited was earlier this year lent £14 million will not come under the scrutiny of the boards. In other words, the Department of Trade and Industry has taken a commendable step towards rationality by setting up the requirements boards but then has reserved to itself the right to act irrationally in circumstances where one of Mr John Davies's lame ducks makes a particularly heartrending plea for special treatment. This, on the face of things, is an arrangement that should be changed. If, for example, the requirements board for computers, systems and electronics is to become, as it should be, the chief source of policy in research and development in these important fields, should it not at least have the power to say that the systems which the computer industry needs could be provided most efficiently by commissioning work in existing laboratories and not by the provision of large sums of money to individual commercial companies?

The financial basis for the conduct of industrial research and development, further details of which are provided both by the Department of Trade and Industry and by the Lord President's office, also calls for further examination. The Select Committee on Science and Technology argued strongly that research and development of potential industrial value carried out with government funds in public laboratories should wherever possible be on a "full repayment basis" and the government now appears to accept this doctrine. But is there not a case for saying that this is not an issue of principle but a question of how the British practice should be related to that in other countries with whose commercial enterprises British companies will in future have to compete? There are many circumstances in which it would seem entirely appropriate that publicly supported research might be undertaken simply because there is reason to think that this is of strategic value for the development of British industry, and where costs might be most appropriately recovered not by full repayment but by means of royalties. Too slavish an attachment to the principle of full repayment may, in other words, prevent the Department of Trade and Industry from acting as a sufficiently vigorous initiator of new projects, to the detriment of its declared intentions. Two particular issues also call for further detailed scrutiny. The proposal that all the non-nuclear work of the Atomic Energy Authority should be channelled through one of the six requirements boards (except when full repayment is assured) may undermine the success of laboratories such as that at Harwell in building up a coherent policy as an industrial entrepreneur of a new kind. It is also worth asking why there is no requirements board for the aircraft industry, which at present consumes the lion's share of the department's expenditure on industrial research and development.

Although the government's response to the Select Committee on Science and Technology is belatedly courteous, there are two general points on which further discussion is needed. First, the government now promises that it will ensure that all industrial research and development laboratories, as well as the requirements boards

themselves, will publish an annual report, and this goes some way to meet the Select Committee's proper demand that much more should be publicly known about the formation of policy on research and development. But are annual reports enough? Everybody knows how easy it is for laboratory directors to pad out their annual reports with lists of accomplishments and, in the process, to avoid questions about the general development of policy. What this implies is that the government will have to keep a vigilant eye on its laboratory directors if the implicit promise to the Select Committee is to be kept. But it is also a pertinent question (which the Select Committee should have raised) whether the contract documents generated under the new arrangements between, for example, government departments and research councils should not themselves be made public.

Another question not entirely resolved by the government's response is whether there does not need to be a more explicit machinery for determining the general pattern of research and development in Britain. The government is right to argue against a Minister for Research and Development, the Select Committee's favourite cause. The truth is that it would be inconsistent to set out, as the government has done, to make the several government departments thoroughly competent at managing their own research and development and then to give a minister with no departmental functions overall responsibility. But the case for an advisory council, working to the Cabinet Office, is stronger than the government admits, if only because the Cabinet Office is necessarily overburdened with day to day matters and therefore less able to make a comprehensive study of national needs and the means of attaining them.

100 Years Ago



M. COLLAS, of Paris, comments in *Les Mondes* of December 12, on M. A. Lallemaunde's paper on the blue colour of the atmosphere, in which it was attributed to a change of refrangibility due to a partial absorption of the chemical or ultra-violet rays. In 1870 M. Collas, in an article in *Les Mondes*, attributed the blue colour of the Lake of Geneva and other waters to the quantity of silice held in solution, which is brought down by the tributary streams from the strata through which they pass. Numerous observations since have induced him to believe that the blue colour of all the water of the globe is due to the same cause. The air everywhere always contains more or less of moisture due to evaporation from the water of the earth, the water thus evaporated always contains a greater or less quantity of extremely fine insoluble particles. Silice, says M. Collas, is one of the most common insoluble substances in nature, and through evaporation, performs the same function in the blue sky that he believes it does in the blue waters of the earth. He believes his theory is confirmed by the intense blue of southern skies, where evaporation is so much greater than in the colder north.

From Nature, 7, 132, December 19, 1872.

University Growth Rate to be Pruned

A LARGE expansion in school education and a reduction in the growth rate of higher education are the key points of the ten-year plan announced last week by Mrs Margaret Thatcher, Secretary of State for Education and Science (*Education: A Framework for Expansion*, HMSO, £0.315p).

A new nursery school programme will provide places for 90 per cent of all 4 year olds and 50 per cent of 3 year olds by 1981. Primary, secondary and special schools will all benefit from larger building programmes and teacher training is to be improved, but the growth in higher education will fall from the present 6.5 per cent a year to 5 per cent a year until 1981.

But although the expansion of higher education may be slower during the next decade than it has been since the Robbins report of 1963, the reduction is hardly a standstill. The number of places in the universities, polytechnics and colleges of education in Great Britain will increase from 463,000 today to 750,000 by 1981, the number divided equally between universities and other forms of higher education.

The polytechnics will expand fastest. By 1981 the polytechnic population will have doubled to 180,000 while the numbers in the colleges of education will increase by only 40,000 to 155,000. The universities, however, will take 139,000 more students than the 236,000 they teach today, an increase of 59 per cent.

The total of 750,000 places by 1981 is, however, lower than the 835,000 places set as the provisional goal for higher education in a Department of Education and Science (DES) document circulated two years ago.

Table 1 University Grants for 1972-77

Academic Year	Recurrent grant* £ million	Equipment grant* £ million
1972-73	252.0	23.5
1973-74	263.0	24.5
1974-75	276.0	25.5
1975-76	292.0	27.0
1976-77	309.0	29.0
	1,392.0	129.5

*1972 prices

Mrs Thatcher's white paper included the long-awaited quinquennial settlement for the universities for the period 1972-77 (see Table 1). The grant for 1972-73 is now finalized at £1.7 million more than the provisional allocation



Mrs Margaret Thatcher, Secretary of State for Education and Science

made to tide the universities through the past year. A further £7.4 million will be paid in 1972-73 to compensate for inflation.

The target for student numbers in 1977 is now 306,000 full-time students,

Two Views of Nature

THE left-hand illustration is a reproduction of page 453 from the issue of *Nature* dated June 23, 1972. That on the right is a reproduction of the corresponding page from the photocopied version of *Nature* distributed (without

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g¹ h¹ of fresh wet tissue. These were withdrawn microscopically and Challenge's experiment would suggest that other species of algae at other seasons are more prolific in their output. The emission of DMS from living intact leaves of oak, cotton, spruce and pine trees ranged from 2 to 43 × 10⁻¹² g of over-dried tissue per hour, the rate of emission for decaying leaves from the same species was 10 to 100 times greater. Whether the metabolism of the leaf is directly responsible for this emission of DMS, or whether it is a secondary result from the microbial populations living on the surface of the leaves, is unknown.

Soil samples were collected in various places in the United States in December and January 1971-1972. All soils produced DMS if contained in flasks sealed with glass wool, allowing reciprocal exchange of gases with the surrounding air (Table 1). If the flasks were completely sealed DMS production fell and hydrogen sulphide was produced. The oxygen content of the sealed flasks fell by c.15, thus showing that aerobic conditions were not responsible for H₂S synthesis. The CO₂ concentrations in the sealed flasks increased to several thousand parts per million. Possibly either the high CO₂ concentrations suppressed the microorganisms synthesizing DMS and/or stimulated microorganisms producing H₂S.

From these experiments which confirm Challenge's work it would seem that DMS is ubiquitous in the biosphere. The quantity of sulphur of biological origin required to balance the sulphur cycle by transfer through the atmosphere is approximately 10¹⁰ tons yr⁻¹ (Table 4). If we assume that this transfer occurs by directly volatilized sulphur, the atmospheric residence time of one week, characteristic of a moderately mobile gas, then the anticipated equilibrium concentration would be 4 × 10⁻¹⁰ parts by volume. The available concentration and the distances from soil and plants. If they are representative, could sustain an atmospheric concentration of the order. We therefore think that DMS may be considered as the candidate compound in the natural transfer of sulphur of biological origin.

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with places for part-time students to the full-time equivalent of 15,500, making a total of 321,500 students occupying 310,000 university places. This figure compares with a provisional planning estimate made by the University Grants Committee in May 1970 of 331,000 students occupying 320,000 places.

By 1977, 254,000 of the 306,000 full-time students will be undergraduates, 47 per cent of which will be arts students and 53 per cent science-based students. The present balance is 55 to 45 in favour of science students.

To meet the increased numbers, the government is to allocate £29 million for the 1974-75 building programme and increase the number of residential places to about 13,000 by 1975. No new universities will, however, be built in the current quinquennium, although the UGC will advise the government on whether an early decision in principle is needed to establish new universities in the 1980s.

The overall effect of the government's plans will be to increase the percentage of 18 year olds entering higher educa-

agreement with the publishers) from Moscow to Russian scientists. The article in the right-hand column was by Dr Zhores Medvedev. It is not known whether sales of HMSO books in the Soviet Union have been substantially increased by this extra insertion of an advertisement.

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tion from 15 per cent in 1971 to 22 per cent in 1981; in 1961 the figure was 7 per cent.

But in spite of the expansion there are one or two warning notes on economy in the government's white paper. Student-staff ratios are to be increased from 8:1 at present to 10:1 by 1981. This transition, the government says, "should be possible without lowering standards". The government is also patently eager to encourage more students to live at home. The number living away from home now is "unrealistic and unnecessary". The government also plans to introduce a 2 year Diploma of Higher Education, available within all the principal sectors of higher education. The DipHE is "not a cheap substitute" for the forms of higher education already available, the white paper says.

Immediate reactions to Mrs Thatcher's package were not all favourable. The Committee of Vice-chancellors and Principals is pleased that universities will be expanding as fast in the current quinquennium as they did in the one just past, but is concerned that while undergraduate numbers will increase by a third, postgraduate numbers will rise by only a sixth. Equally the student-staff ratio of 10:1 is a worry if it is to be applied to universities as well as to polytechnics and colleges of education. Such a ratio could severely hamper research in the universities.

The Association of University Teachers complains that Mrs Thatcher did not consult everyone fully before producing her plans, and states that university places will fall short of demand by 75,000 to 100,000.

RESEARCH AND DEVELOPMENT

Government Replies

DETAILED replies to the four reports on government research and development produced earlier this year by the Select Committee on Science and Technology were given by the government in white papers published last week. (Command 5176 and 5177, HMSO, £0.105 and £0.13.) Sharing the load, Lord Jellicoe answered the select committee's first and fourth reports on research and development policy, and the Department of Trade and Industry replied to the second and third reports on the non-reactor work of the Atomic Energy Authority and the department's industrial research establishments.

Lord Jellicoe's document explains the government's rejection of the select committee's proposal for a minister for research and development in rather more detail than was managed in the cursory two paragraphs devoted to the select committee's views in last July's

white paper. A separate minister for research and development, the government now says, would contravene the principle of functional organization. Each department should be a complete and coherent body and should have all the facilities necessary to do its job, including the right and means to commission the research and development it needs to fulfil its tasks.

Each department must be accountable for the effective use of its money, and a minister could not carry this responsibility if part of his facilities—the right to approve research and development—lay elsewhere.

The government also holds that the "central advisory function" that the select committee proposed for the minister for research and development is already provided by the Chief Scientific Adviser, who advises the Cabinet.

The select committee argued that Britain's entry to the EEC would require "something more coherent than the existing machinery", but the government replies that while entry into the community will lead to more collaboration the same principles—that each minister should be responsible for all his department's efforts—still apply.

The select committee's proposal for a Council for Science and Technology is also rejected largely on the grounds that it is closely tied to the proposal for a minister for research and development.

But one of the select committee's proposals does receive the government's blessing. Government departments will, in future, publish annual reports on their research and development activities. The government is also to publish an annual list of official sources of information on its research and development.

But if Lord Jellicoe's reply offered cold comfort to the select committee, the DTI's answer was marginally more encouraging. The department accepts that the funding of non-nuclear projects commissioned by government departments from the Atomic Energy authority should appear on the department's vote and be listed separately in the UKAE's annual report. It also agreed that more of the Authority's non-nuclear work should be done on a full repayment basis. But the department does not accept that an Industrial Advisory Committee should be set up to keep under review, in cooperation with the new Requirements Boards, the extent and scope of the authority's nuclear and non-nuclear work. Delay and duplication would be the only result of such a board in the department's view.

In reply to the select committee's recommendations that a Research Establishment Authority is needed to give the establishments more indepen-

dence, the government simply argues that in fact fuller integration with the department is what the establishments need, not more freedom under a separate authority.

The reaction of Mr Airey Neave, chairman of the select committee, was predictably cool. "The committee believes," he said, "that with increasingly large national research and development programmes in Europe, the government will have to change its mind about the central organization for research and a minister to direct it."

The select committee will open its work this session by enquiring into the computer industry once more with a view to assessing the impact entry into Europe will have on it, and by completing its work on nuclear reactor policy.

LIFE SCIENCES

New Japanese Institute

by our Special Correspondent

Tokyo, December

THE opening of the Mitsubishi-Kasei Institute of the Life Sciences was celebrated last week in Japan with two scientific symposia on the future of the life sciences which were held in Tokyo on December 4 and Kyoto on December 6. The institute itself, which is housed in a brand-new building 50 km south-west of Tokyo, has been assembling since early November but is unlikely to be fully up to its planned strength of sixty scientists for some months. The director, Dr Fujio Egami, now professor emeritus at the University of Tokyo, says that the annual budget of the new institute is at present the equivalent of \$1.7 million. One striking feature of the employment policy so far is that the number of women scientists on the staff is much higher than in comparable scientific laboratories in Japan.

The new institute was founded in June 1971 to celebrate the twentieth anniversary of Mitsubishi Chemical Industries Limited, but the intention is that it should be concerned entirely with basic research in the life sciences and that its link with Mitsubishi should be that of a recipient with its donor. The institute is at present organized into four departments concerned with the general life sciences, neuroscience, environmental biology and special research. The first of these departments is the most complete and will be concerned with certain basic biochemical problems and in particular with the function of bacteriocins, the comparative biochemistry of enzymes of thermophilic bacteria, attempts to modify the genetic properties of bacteria by the use of specific nucleic acid enzymes and a variety of problems in developmental biology.

NEW WORLD

Under the Shadow of the Axe

from our Washington Correspondent

THERE is a general air of gloom and uncertainty pervading the federal departments and agencies in Washington which have dealings with science and technology, and the mood is unlikely to lighten much in the next few months. The most immediate cause for concern is the likelihood that in the next week or two the Office of Management and Budget will send out an order directing federal officials not to spend some of the money which they have already committed for the present fiscal year. The second cause for gloom is that the season for putting the finishing touches to the 1974 budgets has now arrived, and all indications point towards a period of financial famine. Finally, the much-publicized post-election shake-up of the White House staff had not at the beginning of this week reached the

Office of Science and Technology, but rumours are rampant.

The impending budget cuts for the present fiscal year, which is now halfway through, will be a direct result of President Nixon's much repeated promise to hold federal spending down to \$250,000 million in order not to increase taxes next year. According to a study published last month by the Brookings Institution, he will have to cut about \$6,000 million from existing programmes if he is going to meet the target, but all the cuts must come from programmes which together account for about \$72,000—the rest of the budget goes to relatively uncontrollable items such as pensions and federal salaries.

Unfortunately, programmes involving science and technology are likely to suffer particularly prominently from the Administration's knife, for they nearly all fall in the controllable cate-

gory. The Administration's cost cutting has, in fact, already affected several science programmes which have been approved by Congress—Nixon has twice vetoed the HEW Appropriations bill, refused to sanction bills designed to set up a National Institute on Aging, and to encourage mining research, and he tried in vain to block the Water Pollution Control Bill—but the scientific community clearly faces further belt tightening in the coming months.

If the Office of Management and Budget does hack a large slice off the 1973 fiscal year budgets, the effect would be particularly severe, because some of the cuts would be made in programmes for which grants or contracts have already been let. According to an article in the November issue of *sppsg*, a science policy newsletter published by MIT, the Administration has the power to withhold funds appropriated by Congress under the Anti-Deficiency Act of 1870, but if the OMB's actions lead to a government refusal to honour some contracts let in good faith, it can be safely assumed that such an action would be contested in the courts.

What effect is all this short-term financial stringency likely to have on the 1974 budget, which is due to be unveiled next month? At present, there can be little doubt that academic science is in for a thin time. Federal expenditure during the past three years has been higher than at any time since the Second World War, and the Administration will certainly take some drastic steps to hold it down next year. On the other hand, however, according to the Brookings Institution study, there will be a built-in uncontrollable increase in federal spending next year of some \$20,900 million, including an estimated \$9,200 million increase in social security. Moreover, any hopes that the possible ending of the Vietnam war would lead to a decline in the budget of the Department of Defense were dashed last week when Mr Melvin Laird announced that salary and other cost increases would require a budget for the DoD of more than \$80,000 million.

In the face of such uncontrollable increases in federal expenditure, it therefore seems likely that the controllable items in the budget will be hard pressed. Academic science, which falls in this category, and which also suffers to some extent from the desire for quick payoff, is therefore likely to continue to suffer for some time.

CANCER RESEARCH

MIT Branches Out

from our Washington Correspondent

THE Massachusetts Institute of Technology, for long a bastion of engineering and the physical sciences, is branching out into cancer research in a big way. It was announced last week that the National Cancer Institute has given MIT a grant of \$2,362,500 to help set up a Center for Cancer Research where some 60 professional scientists and technical assistants will eventually work on tumour virology, immunology, cell biology and cell development. The centre, which will be headed by Dr Salvador E. Luria, will be the first major cancer research institution in the United States not directly connected to a hospital or medical school.

Why MIT? One good reason is that the institute itself has provided a building on its East Campus and \$1.8 million towards converting and renovating it. Another is that MIT has, over the past decade or so, built up considerable expertise in cancer research and basic cell biology, with Dr David Baltimore, Dr Phillips Robbins, Dr Alexander Rich and Dr Luria particularly prominent.

Work on reconstructing the building will begin on January 1 next year, and it is hoped that two floors will be occupied by October 1973. The rest should be ready by May 1974 and when

completed, the centre will have about 35,000 square feet of research and office space. The National Cancer Institute will provide \$136,376 for the first year of operation and £1.89 million for 3 more years.

Apart from the appointment of Dr Luria to head the centre, the only other staff member who has so far been confirmed is Dr David Baltimore, who will move his tumour virology research over to the centre next year. Dr Luria also said last week that "a very prominent cancer immunologist" will be joining the centre next year, but his appointment must await confirmation by the faculty board when it meets in January.

Asked last week what type of research will be performed at the centre, Dr Luria said that virology and immunology will be followed in the second year of operation by cell biology and cell development—the thrust of the research will be basic cancer biology and biochemistry. "A man-on-the-moon approach" to cancer research would be appropriate, Dr Luria said, "only when the basic knowledge is available. We do not have that knowledge in cancer—much more basic research is needed". As for clinical studies, Dr Luria said that although none is planned for the first three years of operation, researchers at the centre will be working on clinical materials, mostly supported through the Harvard-MIT Medical Program.

TECHNOLOGY ASSESSMENT

OTA Taking Shape

by our Washington Correspondent

DURING the Congressional close season, Senator Edward M. Kennedy and his staff have been quietly moving behind the scenes mapping out a path for the Office of Technology Assessment—Congress's new think tank and crystal ball on technological matters. If Kennedy gets his way, and he probably will because he will be chairman of the OTA's policy board, the office seems destined to become a powerful force in American science policy, not to mention a base from which Kennedy can launch assaults on the Administration's policies.

Although the legislation which set up the office would seem to prescribe a fairly passive role for the OTA—chiefly that of letting contracts to universities and other organizations for assessments of problems referred to it—Kennedy's plans would make the office highly active. First, the OTA board, which consists of six senators and six members of the House of Representatives, is given the power under the legislation to initiate studies off its own bat, and Kennedy hopes to use that authority to good advantage. He has already asked the National Science Foundation to draw up a list of likely topics for study and has informally asked the National Academy of Sciences for advice on priorities.

Another possibility which would give the OTA considerably more public attention is that the board may hold public hearings from time to time. Moreover, Kennedy and his staff have been considering the possibility of having *ad hoc* panels appointed by the OTA board to study specific issues. One advantage of such an arrangement is that panels could be appointed to draw up reports on issues where timeliness is necessary, for example to affect the passage of a particular item of legislation. Much of the OTA's work will necessarily be in the form of long-term studies, and the ability to appoint such panels for quick, qualitative studies would greatly increase its flexibility.

As for personnel in the office, there are at present two vacancies on the OTA board because neither Senator Gordon Allott nor Representative Earle Cabell were reelected to Congress. At present, Olin Teague of Texas seems to be the most likely candidate for the position vacated by Cabell, but a successor for Allott has not yet emerged from the Republicans. (Teague is expected to become the chairman of the House Committee on Science and Astronautics, unless he gets caught up in the manoeuvring for the House leadership.)

Another important appointment, which will be made when the OTA board has its first meeting in January, is that of director of the office. Kennedy has already had a meeting with Emilio Q. Daddario, former chairman of the House subcommittee on Science, Research and Development, and chief architect of the legislation which set up the office. The indications are that the board will offer the directorship to Daddario and that he will take it.

All Kennedy's plans are, of course, subject to debate and approval by the rest of the OTA board, and the office is, in any case, unlikely to be funded until next spring. If Kennedy does get his way, however, the office will clearly be a powerful body which will make its presence felt in science policy circles. It could also become a thorn in the Administration's flesh as it brings United States science policy under its microscope.

POPULATION

A Hint of ZPG

by our Washington Correspondent

THE US government last week released a set of figures which should bring joy to the hearts of members of Zero Population Growth and others concerned about the so-called population explosion. During the first nine months of this year, the birth rate in the United States fell to 75.3 births per thousand women of childbearing age (between the ages of 15 and 44). If maintained, this birth rate would result in an average of 2.08 children per family, or just below the 2.1 level needed for zero population growth. Even in absolute terms, the number of births dropped during the first nine months of this year, to 2,437,000, compared with 2,673,000 during the corresponding period last year.

Even if the birth rate is maintained at the ZPG rate indefinitely however, the population of the United States would still grow to about 320 million from its present size of about 210 million because the age distribution of the present population is heavily weighted towards younger people. Dr Paul Ehrlich, founder of ZPG, said last week that the decline in fertility is "cheering", but added that "it is extremely important that we get a rate lower than this so that population growth will end sooner".

One way to help push the fertility rate down even further is through an expanded population research programme, and it was announced last week, hard on the heels of the new population figures, that a new Biomedical Center for Population Research is to be established at the University of Chicago, and the Ford Foundation has also announced that it

has awarded twenty-six grants, totalling \$647,702, for studies of population policies. The Chicago centre, which is being set up with a \$436,658 grant from the National Institute of Child Health and Human Development, will support biomedical research into reproduction. The director of the centre is Dr Elwood V. Jensen. The research supported by the Ford Foundation will be sociological studies ranging from the effect of US income tax laws on fertility patterns to the motivations for delayed marriage among the women of Hong Kong.

Short Notes**Medical Ethics**

THE National Institute of General Medical Sciences has awarded a grant worth nearly \$220,000 to the Institute of Society, Ethics and the Life Sciences, for a three-year study of the ethical implications of genetic counselling and of screening for carriers of heritable diseases. The institute, which is based at Hasting-on-Hudson, New York, will look into the general issues of privacy, confidentiality, informed consent and freedom from coercion in genetic counselling and screening. Such issues have recently been brought into the spotlight by the increased attention directed towards screening and counselling for sickle cell anaemia.

Baldeschweiler to Caltech

DR JOHN D. BALDESCHWEILER, Deputy Director of the Office of Science and Technology and Deputy Science Adviser to President Nixon, will leave Washington next July to become chairman of Caltech's Division of Chemistry and Chemical Engineering. Baldeschweiler has been a member of the Office of Science and Technology for almost two years, and before that he was Professor of chemistry at Stanford University. He succeeds Dr George Hammond at Caltech, who resigned last July to become Vice-chancellor of the University of California at Santa Cruz.

Pioneer 10

A RECENT course adjustment to Pioneer 10 should take the spacecraft behind Io, the orange satellite of Jupiter, which will allow measurements to be made of the satellite's atmosphere. Io may have an atmosphere of nitrogen or methane, and as the spacecraft passes behind the satellite, changes in the radio signals cutting through the atmosphere should shed light on its composition. For about ten minutes after Io emerges from Jupiter's shadow, it is much brighter than normal, a phenomenon which may indicate that a temporary deposit of ice forms on its surface when it is cut off from sunlight.

NEWS AND VIEWS

How to Measure Temperature More Accurately

THE precise measurement of the physical quantity "temperature" has occupied the minds and time of metrologists for many years. It is because of the difficulty of making sufficiently precise and reproducible measurements for everyday use that the need for an internationally agreed practical scale has arisen. This scale (the International Practical Temperature Scale of 1968) is based on the properties of such instruments as platinum resistance thermometers, thermocouples and, for high temperatures, optical pyrometers. It is constructed so as to give values of temperature which are close to the more fundamental thermodynamic temperatures.

In principle any measurable parameter can be used as a basis for the definition of thermodynamic temperature if an explicit relationship linking it to kT can be written down. For a gas at low pressure the relationship $pV=NkT$ is perhaps the most familiar, but others, in which kT is related to physical properties such as the velocity of sound in a gas, or the Johnson noise in a resistor, or the spectral or total thermal radiation from a blackbody, have been used. One of the chief problems has always been that of devising a method and experimental technique which avoids errors resulting from the non-ideal behaviour of real physical systems. For example, the simple relation $pV=NkT$ holds for a real gas only in the limit as the pressure falls to zero and, again, the Planck law of radiation strictly describes only the thermal radiation existing inside a closed cavity whose dimensions are very large compared with the wavelength. It is for this reason that the article by Gebbie, Bohlander and Futrelle on page 391 of this issue of *Nature* raises some interesting possibilities.

Gebbie *et al.* propose that thermodynamic temperature could be determined with useful accuracy from measurements of the spectral distribution of radiation emitted from a near-blackbody cavity. In principle this method, which depends upon an *a priori* knowledge that the emission is Planckian, can also give information concerning the departure from ideal behaviour of both the radiator and the detector provided that sufficient data are obtained. The novelty in the proposal lies both in the application of Fourier transform spectroscopy to the collection of the data and in the way in which the data are treated mathematically.

It is well known that for a blackbody, or a surface of known emissivity, a single measurement of intensity at a known wavelength is sufficient to specify the temperature. This is the basis of the simple optical pyrometer. If the source being observed is not a blackbody, yet is known to have an emissivity which is the same at two particular wavelengths, then a measurement of the ratio of the intensities at these two wavelengths will yield the temperature. This is the principle of the so-called "two colour" pyrometer. If the emissivity varies linearly with wavelength then measurements at three wavelengths will suffice, and so on, until the situation is reached in which the emissivity varies as the n^{th} power of the wavelength

for which measurements at $n+2$ wavelengths lead to the temperature. This principle of the "multi-colour" pyrometer has not generally been considered a practical method because, to give an acceptable accuracy, very high precision in intensity measurement is called for.

Gebbie *et al.* are, however, proposing to use the high spectral resolution and efficiency of a Michelson interferometer to provide information at a large number of wavelengths. The high efficiency of the interferometer allows much redundant information to be obtained quickly, and they are proposing to take advantage of this information in sophisticated iterative computational procedures which can, on the principle of the "multi-colour" pyrometer, take account of departures from ideal behaviour of the radiator, the optical system and the detector. The observed data are in the form of an interferogram, which is the Fourier transform of the spectral distribution of the source combined with a function describing the spectral transmission and sensitivity of the instrument.

In spite of its attractions, the method of Gebbie *et al.* is not without practical difficulties. As the authors point out there is the problem of finding a detector which is sensitive over a very wide wavelength range yet which is linear over a dynamic range of at least 5,000:1. Another problem not considered by the authors but familiar to physicists faced with making very precise measurements of long wavelength thermal radiation is that of diffraction. It may be necessary to take into account the variation in the instrument function resulting from diffraction losses which vary with both wavelength and path difference. It may well be possible to take these into account, for there is a large amount of redundant information available, but it is by no means clear from the preliminary error analysis of Gebbie *et al.* that in so doing unacceptable demands will not be placed upon the accuracy required in the power measurements.

These difficulties notwithstanding, Gebbie *et al.* are surely right in re-emphasizing the importance of trying to use thermal radiation techniques down to lower temperatures than have previously been thought feasible. This point of view came out very clearly at the Fifth Symposium on Temperature held in Washington in June 1971. Some results of new gas thermometry and total radiation thermometry were presented from the National Bureau of Standards which cast doubt on the knowledge of thermodynamic temperature even in the region of the steam point. This important fixed point of temperature had previously been ascribed the value of $100^\circ\text{C} \pm 0.005^\circ\text{C}$ by the Consultative Committee on Thermometry of the International Committee of Weights and Measures. The new gas thermometer measurements indicate a steam point temperature some hundredths of a degree lower than this. Preliminary results of total radiation measurements also indicate a somewhat lower temperature.

It is of interest to compare the proposal of Gebbie *et al.* with the radiation work of the NBS and similar

work now in progress at the National Physical Laboratory, Teddington. The method adopted by the two standards laboratories has been to make simple ratio measurements of the total radiant power emitted by two blackbodies, one of which is at the reference temperature of 273.16 K (0.01° C). For a measurement at the steam point the ratio is about 3.5 to 1. Although it is true that a disadvantage of this method compared with that pro-

posed by Gebbie and his colleagues is that the two radiators must be very close approximations to blackbodies, this must be set against the fact that the dynamic range required of the detector is very much smaller. Whatever the merits of the two methods of approach it seems certain that one way or another the classical gas thermometer is going to be challenged as the arbiter of thermodynamic temperature.—From a Correspondent.

Prostaglandins, Pain and Fever

ASPIRIN and aspirin-like drugs have been used in medicine for about a century. They are used clinically for their anti-inflammatory, analgesic and antipyretic effects. "Aspirin is now used by the ton, and sold under a variety of names" wrote Gaddum about 30 years ago. Yet if one looks in any textbook of pharmacology to find out something about the mechanism of action of aspirin and aspirin-like drugs, one is left with a blank. There are descriptions of their therapeutic effects, their side and toxic effects, and one is perhaps also told that the analgesia is partly a peripheral, partly a central effect due to an action on supraspinal structures, and that is the end of it. No word of how these substances produce their effects.

The situation changed completely when, in 1970, Vane and his colleagues at the Royal College of Surgeons made the fundamental discovery that aspirin and aspirin-like drugs inhibit an enzyme, the synthetase which synthesizes prostaglandins from the unsaturated fatty acid, arachidonic acid, a physiological precursor of some prostaglandins. Is the relief of symptoms by aspirin and aspirin-like drugs therefore attributable to inhibition of prostaglandin synthesis? That was the problem on which Vane and his colleagues, as well as others, at once began to work.

The anti-inflammatory action can be readily explained by inhibition of prostaglandin synthesis. Prostaglandins are found in inflammatory exudates and produce an inflammatory response on intradermal injection. It is more difficult to assess their role in pain production, because they do not produce much pain when injected intradermally or when applied on a "blister base" unless applied in abnormally strong concentrations. On the other hand, headache occurs on their intravenous infusion in man, and Collier has shown that an intraperitoneal injection into mice produces a writhing response.

Ferreira has now re-examined the pain producing effect of prostaglandin E_1 (PGE_1). Two of his findings, which he reports in this week's issue of *Nature New Biology* (240, 200; 1972), may give a clearer understanding of the role of prostaglandins as pain mediators in inflammatory reactions, because they suggest that the principal action of prostaglandin is not to produce overt pain but to sensitize the pain receptors. The method he used was to introduce the prostaglandins by slow subdermal infusion into the volar surface of the arm and to infuse it in concentrations as weak as those found at the site of an inflammatory reaction. The first sensation felt was relatively modest overt pain, but the real interest lay in the development of a long-lasting hyperalgesia—pain elicited only when slight pressure was applied to the

infusion area—and in an increased pain sensitivity to chemical stimuli such as histamine or bradykinin.

The development of hyperalgesia was dependent not only on the concentration of PGE_1 infused, but also on the duration of the infusion. This suggests that a continual release of minute amounts of prostaglandin in an inflammatory site will gradually produce a hyperalgesic state. Aspirin does not alter the hyperalgesia caused by a subdermal PGE_1 infusion. Nor should it do so if its action is solely attributable to inhibition of synthesis of prostaglandins because it would then not prevent the effect of infused prostaglandin.

The increased pain sensitivity to chemical stimuli was demonstrated by subdermal infusion of PGE_1 together with histamine or bradykinin or with both substances. Under these conditions, strong pains developed which became continuous towards the end of a 30-minute infusion. Similarly, pain of gradually increasing intensity developed when histamine, and particularly when bradykinin, was infused into a hyperalgesic site produced by a previous infusion of PGE_1 . Release and/or formation of histamines and bradykinin take place in an inflammatory site so that their direct excitatory effect on pain receptors would become intensified by the sensitizing action which the continuously-released prostaglandins would have on these receptors. Aspirin and aspirin-like drugs would then alleviate the pain because they inhibit this continuous release as they inhibit prostaglandin synthesis.

A second contribution on the subject, by Flower and Vane, appears on page 410 of this issue of *Nature*, and concerns the antipyretic effects of aspirin-like drugs. This story actually began to unfold before Vane made the discovery that these drugs inhibit prostaglandin synthesis. Milton and Wendlandt at the School of Pharmacy, London, had found that minute doses of PGE_1 injected into the third cerebral ventricle of unanaesthetized cats produce fever. This fever, they found, was not affected by paracetamol (4-acetamidophenol) which prevented and abolished the fever produced by injection of a bacterial pyrogen into the third ventricle. They therefore concluded that antipyretics are not antagonists of prostaglandins but that they may act by inhibition of their release.

The problem of prostaglandin fever was taken up by Feldberg and Saxena (1971) at the National Institute for Medical Research. They found that PGE_1 had the same pyrogenic effect in rabbits and rats as in cats, and that the action was on the anterior hypothalamus, the site where pyrogens act when producing fever. This suggested that pyrogens do not act directly on this part of the brain, but through release of prostaglandins in the

anterior hypothalamus. To test this theory, Feldberg and Gupta (1972) collected samples of cerebrospinal fluid (CSF) from the third ventricle in unanaesthetized cats. This CSF must have been in close contact with the anterior hypothalamus which lies in the wall of this ventricle. The samples were tested for PGE₁-like activity on the rat stomach fundus strip preparation to find out if there would be an increase of this activity in CSF collected during a pyrogen fever. Some such activity was detected in controlled samples, but it increased several-fold in samples collected during fever produced by the injection into the third ventricle of a small amount (75 µg) of the bacterial pyrogens *Shigella dysenteriae*, and when the fever was brought down by an intraperitoneal injection of paracetamol, the PGE₁-like activity of the CSF became low again. So here was the first direct experimental evidence for the theory that pyrogens might act by increasing synthesis and consequently the release of prostaglandins in the anterior hypothalamus, and that the antipyretic action of paracetamol was due to inhibition of this synthesis.

More recently, the workers from the School of Pharmacy and from the National Institute for Medical Research joined forces. They found that it was not necessary to collect CSF that had been in close contact with the anterior hypothalamus, that is, CSF from the third ventricle. The same result was obtained with CSF collected from the cisterna magna (Feldberg, Gupta, Milton and Wendlandt, 1972). Its PGE₁-like activity increased many-fold when collected during pyrogen fever, and not only when the pyrogen had been injected into the third ventricle or into the cisterna magna but also when it had been injected intravenously, although about one thousand times larger amounts of the pyrogen were required to produce fever and to increase the PGE₁-like activity in the CSF on intravenous injection, than on injection into the liquor space. And again the fever and the PGE₁-like activity of the CSF were brought down by the intraperitoneal injection of an antipyretic. This was shown not only for paracetamol, but also for indomethacin and aspirin.

PGE₁ contracts the rat fundus strip preparation and the PGE₁-like activity of the samples of CSF were assayed on this preparation by comparing the contractions they produced with those produced by known amounts of PGE₁. But PGE₁ is not the only prostaglandin which contracts the rat fundus strip (Cocconi and Wolfe, 1966; Vane, 1967). The activity could have been attributable to PGE₁, PGE₂, PGF_{1α}, and PGF_{2α} or to a mixture of them. Only PGE₁ and PGE₂, however, produced fever (Milton and Wendlandt, 1971) and when samples of cisternal CSF collected during pyrogen fever were subjected to thin layer chromatography, the activity was found to be present solely in the zone corresponding to the position of the prostaglandins of the E series (Feldberg, Gupta, Milton and Wendlandt, 1972). Because only E₁ and F_{2α} have been identified in cat's brain (Horton and Main, 1967) and because the CSF was obtained from cats, its activity was most likely attributable to PGE₁, though to be certain it would have to be identified by mass spectrometry.

The origin of the PGE₁ detected in the fever samples of cisternal CSF is not clear. Most of it was probably not derived from the region of the anterior hypothalamus but derived from the surface of the brain stem or of

other parts of the brain. If so, this would imply that the action of a pyrogen is not confined to the anterior hypothalamus but that pyrogen increases synthesis and release of prostaglandins anywhere in the central nervous system, though to produce fever it has to act on the anterior hypothalamus. This poses the intriguing question of whether some of the symptoms of high fever, like malaise, are actually the result of high temperature. Instead, they may be effects of prostaglandins acting on other parts of the central nervous system—or even outside it.

All these results seemed to provide good experimental evidence for the theory that a prostaglandin, probably of the E series, is the mediator of the fever response to pyrogens, which is the fever of infectious diseases, that pyrogens increase synthesis and subsequent release of prostaglandins, and that antipyretics bring down fever because, as demonstrated by Vane, they inhibit the synthesis of prostaglandins. There was, however, one result which did not fit this general conclusion. Paracetamol, an antipyretic and analgesic drug which lacks the anti-inflammatory action of aspirin, brought down not only the pyrogen fever but also the associated high PGE₁ activity in the CSF. Yet paracetamol has been found to have very little effect on the synthetase. This anomaly has now been cleared up. The very weak inhibitory effect of paracetamol had previously been demonstrated with dog's spleen synthetase, but when Flower and Vane tested its effects on the synthetase system of rabbit's and dog's brain, they found that the paracetamol was about as active in inhibiting the enzyme as sodium aspirin. It would thus seem that those aspirin-like substances which lack the anti-inflammatory effect inhibit the synthetase system only in the central nervous system and not in peripheral tissues.

A good start has certainly been made following Vane's prediction at the beginning of the year that the demonstrated relationship between prostaglandins and the aspirin-like drugs is likely to set off a "research cascade" of its own.—From a Correspondent.

Isotopes in Meteorites

MUCH of what is known about the early development of the solar system, particularly with regard to the time scale, comes from a study of natural isotope abundances. Two articles in recent issues of *Nature Physical Science* are concerned with isotopic measurements in meteorites. The one by Gale *et al.* (*Nature Physical Science*, **240**, 56; 1972) was concerned with the composition of lead isotopes in ordinary chondrites and that by Manuel *et al.* (*Nature Physical Science*, **240**, 99; 1972) with the composition of xenon in carbonaceous chondrites.

Modern radiometric estimates of the age of the Earth and the solar system date back almost twenty years to the measurements by Patterson on the isotopic composition of lead in meteorites. Current estimates are based on essentially three methods involving the decay of ²³⁵U and ²³⁸U to ²⁰⁷Pb and ²⁰⁶Pb respectively, the decay of ⁸⁷Rb to ⁸⁷Sr and of ⁴⁰K to ⁴⁰Ar. Of these the method involving the decay of ⁸⁷Rb is presently the most powerful following important advances in technique pioneered by Wasserburg

and his colleagues at the California Institute of Technology. These technical advances have involved order of magnitude improvements in the accuracy with which the relevant isotope ratios can be measured and also the reduction to negligible proportions of laboratory contamination of samples by terrestrial Rb and Sr. Wasserburg has been able to date precisely the formation times of individual meteorites and to begin the task of unravelling the early time sequence of meteorite development.

The ^{40}K - ^{40}Ar dating technique gives less precise estimates of meteorite ages because of the problems of diffusive loss of the ^{40}Ar in a large number of samples. A modified technique involving neutron activation, the ^{40}Ar - ^{39}Ar method, promises to provide a solution to this problem, but has so far not been applied systematically to meteorites with low loss of ^{40}Ar .

The work of Gale *et al.* represents a re-examination of the uranium-lead chronology, making use of the recent improvements in analytical techniques to determine accurately the Pb isotope ratios. Because two parent isotopes of the same element are involved in the U-Pb decay scheme it is possible to determine ages by comparing either the appropriate U-Pb ratios or Pb-Pb ratios alone. The estimate by Patterson of the age of the solar system (4,600 million years) was based for technical reasons on the Pb-Pb scheme. The amount of U in the samples is used as a check for consistency and it has been known for some time that in many meteorites there is in fact insufficient uranium to account for the observed development of radiogenic lead. Gale and his colleagues have based their measurements on the Pb-Pb scheme, but have also been able to determine concentrations of U in the identical samples, thus avoiding problems associated with the extremely heterogeneous distribution of uranium. Their preliminary data indicate features of the Pb-Pb chronology of meteorites which were not apparent in the earlier and less precise work. As well as confirming the lack of sufficient uranium, they find that the Pb ratios in the meteorites analysed do not fall on the single linear array found by Patterson on the Pb-Pb development diagram. A linear array would correspond to the most simple history, in which the meteorites concerned were formed at the same time and had subsequently remained closed systems with regard to their uranium and lead content. In view of the Rb-Sr work and the disturbances to the K-Ar "clock" in meteorites it would be expected that more precise Pb-Pb measurements would indeed show departures from the simple "isochron" picture. It remains now for future work to elucidate the detailed significance of these departures.

Xenon isotopes have provided clues to the early history of solar system formation since the discovery by Reynolds in 1960 of anomalous amounts of ^{136}Xe , the daughter product of ^{129}I , in meteorites. ^{129}I is short lived in geological terms, with a half-life of 17 million years, and Reynolds's discovery was interpreted as indicating the presence in the primitive solar system of ^{129}I left over from an earlier period of synthesis of stellar elements. That the ^{129}I was still extant when meteorites formed has been used to infer a time period of (100 ± 50) million years between the onset of collapse of the primitive solar nebula (isolation from element building) and the formation of solid objects within the solar system.

Smaller isotope anomalies in the heavy xenon isotopes

in ordinary chondrites and basaltic achondrites have been interpreted in terms of the presence of the fission decay products of ^{244}Pu , which, like ^{129}I , no longer exists naturally because of its short half-life of 80 million years. This interpretation, based on a great deal of circumstantial evidence, was finally confirmed in 1971 when Reynolds determined the composition of xenon which had accumulated over a two-year period in a 10 mg sample of artificially produced ^{244}Pu . As with ^{129}I , the presence of ^{244}Pu has implications for the chronology of the formation of the solar system, and, taken with the abundances of the natural radioisotopes of U and Th, places constraints on the history of element synthesis.

Two important problems obstruct a full understanding of the implications of the xenon isotope measurements. There seems to be an overall fractionation of the xenon isotopic pattern in meteorites and the Sun by comparison with the terrestrial atmosphere. This fractionation pattern is superimposed on the nuclear effects and is much larger in xenon than in the lighter rare gases krypton and argon. In addition a small group of meteorites, the carbonaceous chondrites, which are thought by many to be particularly primitive objects, contain a xenon component with the characteristics of a fission decay product—large amounts of neutron rich isotopes—but with a composition distinct from xenon from ^{244}Pu .

Of the possible sources for this excess of heavy xenon, the suggestion which has aroused most interest is that it has resulted from the fission of a relatively long lived super-heavy element which may have been formed by element synthesis in an island of stability in the mass region near $A=300$. The presence of the decay products of this element in carbonaceous chondrites but not in ordinary chondrites is to be understood in terms of its volatility, which one proponent of the theory has estimated to be comparable to lead or bismuth.

The article by Manuel *et al.* deals with the xenon pattern in carbonaceous chondrites in the light of some recent measurements in which very large isotope anomalies, up to 40 per cent in ^{136}Xe , have been observed. The significant feature which they find is a correlation of the heavy isotope anomalies with light isotope anomalies, shown clearly in their plot of $^{124}\text{Xe}/^{130}\text{Xe}$ against $^{136}\text{Xe}/^{130}\text{Xe}$. A linear correlation of the form observed is usually interpreted as a mixing line between two components which define the end points of the line. Manuel *et al.* point out the difficulties of devising an *in situ* nuclear process which will produce the anomalous component enriched in both heavy and light isotopes. A composite of xenon from nuclear fission with fractionated "normal" xenon would fit the observed pattern, but if this explanation, put forward many years ago, is still to be accepted the mixing of fractionated and fission xenon must have occurred before the xenon was introduced to the meteorite in order for the heavy and light anomalies to be correlated now.

The observation seems to rule out an *in situ* nuclear origin for the anomalies, and in so doing makes the quantitative inferences concerning super-heavy elements more tenuous. Manuel *et al.* put forward other possible explanations of the anomalies including the exotic suggestion that they may represent the remnants of a supernova or alternatively a combination of mass fractionation plus high flux neutron-induced fission of ^{235}U during the Sun's deuterium-burning stage.—G. T.

Nuclear Genes code Mitochondrial RNA Polymerase

THERE is now a great deal of evidence to support the idea that mitochondria in all probability evolved from some symbiotic bacteria-like organism. Several biochemical vestiges of the bacterial ancestry of mitochondria have been revealed, and in particular it is known that the protein-synthesizing machinery in mitochondria resembles that of bacteria both in its molecular composition and in its response to various antibiotics. It has become equally obvious, however, that mitochondria rely to a considerable extent on nuclear genes, nuclear RNA polymerase and cytoplasmic ribosomes for the synthesis of at least some mitochondrial proteins, including apparently mitochondrial RNA polymerase. That this mitochondrial enzyme is specified by a nuclear gene is the interesting conclusion of the experiments reported in *Nature New Biology* last Wednesday (240, 195; 1972) by Barath and Küntzel.

Last year Küntzel and another colleague, Schäfer, reported isolating an RNA polymerase from the mitochondria of *Neurospora crassa* which proved to be quite distinct from the RNA polymerases in the nuclei of this fungus. The mitochondrial enzyme, which is resistant to α -amanitin but sensitive to rifampicin, is, compared with most known RNA polymerases, a very simple molecule, composed of a single species polypeptide which has a molecular weight of about 64,000. Barath and Küntzel set out to discover if this enzyme is coded by a mitochondrial or by a nuclear gene by exploiting two drugs, ethidium bromide and chloramphenicol, which selectively inhibit transcription and/or translation of mitochondrial DNA.

When *Neurospora crassa* is grown in the presence of chloramphenicol, which does not inhibit cytoplasmic translation, growth of the fungal hyphae is inhibited by about 50 per cent but the synthesis of mitochondrial RNA polymerase is not inhibited. This enzyme must therefore be synthesized by cytoplasmic, not mitochondrial ribosomes, but that does not of course rule out the possibility that it is coded by mitochondrial DNA.

Ethidium bromide, which induces mitochondrial petite mutants, blocks

repair and transcription of mitochondrial DNA but not nuclear DNA. When *N. crassa* are grown in the presence of this drug, mitochondrial RNA polymerase is still synthesized. Indeed it seems to be synthesized in a considerable excess, for paracrystalline bodies appear in the cytoplasm which contain a protein that co-migrates on electrophoresis with RNA polymerase extracted from mitochondria. These results can only mean that the structural gene for mitochondrial RNA polymerase is located on a nuclear chromosome, not on the mitochondrial DNA, and they imply more than that. When transcription of mitochondrial DNA is blocked, the transcription of the nuclear structural gene for mitochondrial RNA polymerase seems to be released from some regulatory mechanism which normally restricts the extent of its expression. As Barath and Küntzel speculate, a mitochondrial gene product may act as a repressor of this and other nuclear genes which specify molecules

destined to migrate to mitochondria.

They propose the following fascinating model of the biogenesis of mitochondria. Various mitochondrial enzymes and structural proteins are, they suggest, made in a cytoplasm by translation of messages from the nucleus. These proteins migrate to the mitochondria and induce the expression of the mitochondrial genes, one product of which is a repressor that migrates back to the cell nucleus and selectively inhibits the expression of those nuclear genes specifying mitochondrial proteins. Once the pool of mitochondrial proteins that were made in the cytoplasm is exhausted the biogenesis of the mitochondria ceases until depression of the nuclear genes occurs during the S-phase of the cell cycle. This model tidily accounts, among other things, for such observations as the synchronous division of mitochondria in *N. crassa* and alternate bouts of mitochondrial and nuclear DNA synthesis in HeLa cells.—From our Cell Biology Correspondent.

Discontinuous DNA Replication *in vitro*

ANYBODY interested in the biochemistry of DNA replication should find next Wednesday's issue of *Nature New Biology* (December 20) particularly interesting reading; it contains three reports—two from Bonhoeffer's group and one by Lark—which shed new light on the mechanism of chain initiation and provide a model which unifies a variety of disparate observations of discontinuous and continuous synthesis of DNA strands. Because all known DNA polymerases require a primer with a free 3' hydroxy group available to make a phosphodiester bond and because the two chains of a parental DNA molecule have opposite chemical polarities one of the daughter chains has to be synthesized discontinuously as a series of so called Okazaki pieces while the other may be synthesized continuously or discontinuously.

Olivera and Bonhoeffer suggest that the size of the intermediates produced during replication of DNA depends on competition between two events, propagation of chains already initiated and initiation of new chains. If the rate of initiation greatly exceeds the rate of propagation the intermediates of progeny DNA strands will tend to have a smaller size than when the rate of

propagation exceeds the rate of initiation.

Olivera and Bonhoeffer in fact have evidence that as the rate of DNA synthesis in an *Escherichia coli in vitro* system is reduced and ligase is inhibited the size of the discontinuous chains is indeed reduced. Herrmann, Huf and Bonhoeffer, in their second report, describe experiments which show that the short and long fragments of DNA made *in vitro* by their *E. coli* DNA synthesis system do not self-hybridize but cross-hybridize. They conclude therefore that the intermediates of the replication of one strand are short DNA pieces and that the other strand is synthesized as a series of much longer intermediates.

Finally, Lark reports experiments with temperature sensitive mutants of the so-called small *dna G* locus which clearly indicate that this locus controls initiation of synthesis of Okazaki pieces. When the locus is inactivated ligase is inhibited, no new Okazaki pieces are initiated and chains already initiated increase in length until propagation ceases in the absence of new initiation. These observations are clearly compatible with Olivera and Bonhoeffer's model.

TRANSFER RNA

One State or Many

from our Molecular Biology Correspondent

THE notion of native and denatured conformations, comparable in terms of base pairing, but differing widely in biological activity, occupies a prominent position in the transfer RNA canon. An adroit attempt to sink a pick in its foundations has nevertheless been made by Biltonen and his colleagues. Their reasoning, based on thermodynamic analysis, is economical and persuasive, and probably wrong withal. The conclusion will not, at all events, much commend itself to workers in the field because of the mass of extant evidence, attesting to the existence of more than one monomeric folded state, but it quite clearly deserves a serious hearing.

In the first place, Levy, Rialdi and Biltonen (*Biochemistry*, **11**, 4138; 1972) have compared equilibrium parameters extracted from optical melting profiles of yeast phenylalanine tRNA with the results of calorimetric measurements. On the assumption that the thermal melting curve represents a two-state process, the fractional change in absorbance at each temperature gives an operational equilibrium constant and free energy of melting, and the van't Hoff relation then leads to a corresponding enthalpy. The latter agrees well with the calorimetric value, thus fulfilling one of the criteria for a two-state process. There are other criteria: the independence of the apparent equilibrium constants of the wavelength of the measurements from which they are derived, in spite of the different sensitivities of different wavelengths to the melting of A-U and of G-C base pairs; a first-order rate plot for the melting process; and the absence of discontinuities in the van't Hoff plot. The latter is curved, rather than linear, however, indicating an appreciable heat capacity change on melting (just as is commonly found in the denaturation of globular proteins). The two-state scheme is purely thermodynamic of course, for it does not preclude short-lived intermediates, nor the coexistence of optically indistinguishable substates.

So far, so good—though there is already a head-on conflict with earlier work, reporting multiphasic melting profiles—but the provocative part of the analysis now follows. Levy *et al.* say that the introduction of magnesium ions displaces the melting curve towards higher temperatures, in the familiar manner, but in no way modifies the two-state scheme. It has been reported further that the enthalpy of interaction of the tRNA with magnesium is essentially zero, and that it is not accompanied by any appreciable absorbance change. The vanishingly low enthalpy is equated with the absence of any con-

formational change on binding of magnesium. On these grounds the authors feel that it is unnecessary to postulate anything more than stabilization of the structured relative to the melted state by preferential binding of magnesium.

Levy and Biltonen develop this view in their second article (*ibid.*, 4145). Using their earlier data for the number of magnesium binding sites in the native and melted states, complete with binding constants for the two classes of sites, and their own values for the thermodynamic parameters of melting, including a heat-capacity term, they can satisfactorily simulate the melting characteristics as a function of magnesium concentration. An interesting consequence of their model is that the entropy of melting, and in consequence also the free energy, change sign at about 16° C (in the absence of magnesium), so that low temperature would be predicted to destabilize the structure. They then go on to suggest that the "denatured" state, of low activity, described by Fresco and by Sueoka and their colleagues is nothing more than a mixture of folded and melted molecules, the latter kinetically trapped at the low temperatures by the large activation barriers to refolding. On heating, the barrier is surmounted, and refolding ensues. The magnesium in any case is supposed not to affect the conformation. The burden of proof lies heavy on the authors, however, for they

have to shrug off fractionations of native and denatured forms of tRNAs, on columns for example, one component being active, the other scarcely so, even though their optical properties differ little; also the different nuclease digestion patterns, which are not readily explained in terms of mixtures of states. The most explicit results on these lines have recently been described by Streeck and Zachau (*Europ. J. Biochem.*, **30**, 382; 1972). The argument may ultimately hinge on how different two states may be conformationally, and yet be thermodynamically equivalent within reasonable experimental error. If, as Fresco and his colleagues suggest, the native and denatured states do not differ widely in base pairing, they could well be near-degenerate in enthalpic terms.

Just failing to make direct contact with Levy and Biltonen, because the ionic conditions are not directly comparable, and the tRNA is not the same species, is a group of three articles by Crothers *et al.* What they find, however (Cole, Yang and Crothers, *Biochemistry*, **11**, 4358; 1972), is that several purified tRNAs give multiphasic melting curves at high salt concentrations. In terms of transitions that depend on ionic strength and temperature, phase maps can be compiled. These indicate that the molecules can exist in four conformational states, one of which, in the high-salt and low-temperature range, is the native molecule, and another the

Role of Poly I in Interferon Induction

THE synthetic polyribonucleotide poly I:C is an effective interferon inducer *in vivo* and *in vitro*. In investigations to determine what criteria of molecular structure are necessary for interferon induction, it has an advantage over natural RNAs in that the structure of its strands may be altered and the effects of compounds of varying molecular weights can be found.

During the past two years there have been several conflicting reports on whether the respective sizes of the poly I and poly C moieties affect the biological activity of poly I:C. Probably one of the difficulties in this field is that neither the same systems nor the same methods for molecular weight determinations are used. Two recent reports, however, indicate that it is the size and intactness of the poly I strand which are important for the biological activity of the complex.

Mohr, Brown and Coffey, in next Wednesday's *Nature New Biology* (December 20), report their investigations on the relation between the size of poly I when complexed to poly C for the induction of interferon and also for affecting the survival time of mice injected with leukaemia cells. They found that it was the size of the poly I

moiety and not the poly C moiety which was the crucial factor. Poly I affects the stability of the complex to a much greater extent than poly C: a decrease in the size of poly I decreased the T_m of the complex significantly, whereas a similar decrease in the size of poly C had very little effect. These results are in close agreement with those obtained by DeClerq and DeSomer (*J. Virol.*, **9**, 721; 1971).

Carter *et al.* (*J. Mol. Biol.*, **70**, 567; 1972) used poly I:C, in which one of the strands was interrupted by unpaired bases for interferon induction, and found that if the C strand was affected the complex was still active, whereas if the I strand was affected there was very little activity. The T_m 's of these modified complexes were well above the incubation temperatures of the experiments, and protection of the complexes from nucleases using polylysine did not increase the activity so that it seems that neither thermal stability nor nuclease resistance are the only criteria involved in interferon induction, as has sometimes been suggested. Further investigations on the importance of the poly I moiety of poly I:C may help to elucidate the mechanism of interferon induction.

fully melted species. Magnesium favours the native form, but does not specify any unique conformational state that sodium ions at sufficiently high concentration cannot also stabilize. This proposition indeed has recently been convincingly demonstrated by Goldstein, Stefanovic and Kallenbach (*J. Mol. Biol.*, **69**, 217; 1972). Addition of salt to the tRNA at low ionic strength elicits an optical transition, characterized by high activation energy, and thus implying a structural upheaval.

Cole and Crothers (*Biochemistry*, **11**, 4368; 1972) support these results with temperature-jump kinetics of melting, which reveal two relaxation times (both measured in terms of the absorbance of a single base, thiouracil), the slower of which becomes apparent only at higher temperatures. That both reactions involve melting of predominantly A-U pairs is inferred from the wavelength-dependence, and specific structural changes are tentatively assigned to both of them by a number of circumstantial lines of reasoning. These are melting of the stem of the dihydrouracil loop, and the relaxation of the tertiary structure as a whole. Yang and Crothers (*ibid.*, 4375) also compare the optical profiles, and kinetics of melting, of two *Escherichia coli* tyrosine tRNAs, and from the known sequence differences are able to put forward some very reasonable conjectures on the nature of the two non-native folded states.

GRAVITATION

Quantization Pursued

from a Correspondent

THE very difficult and subtle problem of quantizing the gravitational field was the subject of a conference sponsored by the Physics Department of Boston University and held in Boston from October 31 to November 3. The difficulties which arise include not only the usual technical ones inherent in any quantum field theory but also conceptual problems of a deep nature which touch on the fundamental structures of both general relativity and quantum mechanics.

The conference opened with a talk by Dr C. J. Isham (Imperial College, London), who outlined some of the different technical approaches that have been invented. This was followed by two sessions led by Professor A. Komar (Yeshiva University) and Professor P. G. Bergmann (Syracuse University), who discussed the application of conventional canonical quantization procedures to general relativity. This involves removing from the gravitational metric tensor field those components which correspond merely to choice of space-time coordinate and also (in prin-

ciple) explicitly solving those four of the ten Einstein equations which merely constrain the initial Cauchy data. Canonical commutation rules are then imposed on the remaining dynamical degrees of freedom. The important problem of solving these constraint equations was also discussed by Dr J. York (Princeton University) who showed how his new technique, which involves the use of the conformal geometry of space, could be used.

Canonical quantization is not manifestly invariant under most of the groups which are relevant to general relativity. This defect is partially overcome in the covariant quantization scheme, and this approach, which is the one most like conventional Lorentz-invariant quantum field theory, was surveyed by Professor B. DeWitt (University of Texas).

Another canonical approach is possible in which the constraint equations are not solved classically but are imposed as operator constraints on the quantum state vector. This point of view, which leads to the notions of "superspace" and quantum fluctuation of three geometries, was described by Professors K. Kuchař and J. A. Wheeler (Princeton University). Professor Wheeler went far beyond just the technical aspects and considered some of the deep conceptual problems which

are intrinsic to quantum gravity. He also developed the theme that the structure of space-time could only be understood in terms of the structure of elementary particles rather than the converse statement which he has advocated for many years.

All of these schemes aim at obtaining a complete theory, but in recent years much work has been carried out on model theories in which only a few of the classical degrees of freedom undergo quantum fluctuation. Professor C. W. Misner (University of Maryland) spoke on these model "quantum cosmologies" and presented some new results on a system in which infinitely many degrees of freedom of the universe are quantized.

A number of less conventional attitudes towards the quantization programme were presented, and in particular Professor P. A. M. Dirac (Florida State University) discussed the possibility that the macroscopic and microscopic (atomic size) metric tensors might be different. Professor R. Penrose (Birkbeck College) outlined the current position of his rapidly developing Twistor Theory, and Professor D. Finkelstein (Yeshiva University) presented an intriguing account of his "space-time code" approach to the quantum nature of space-time.

The general impression gained from

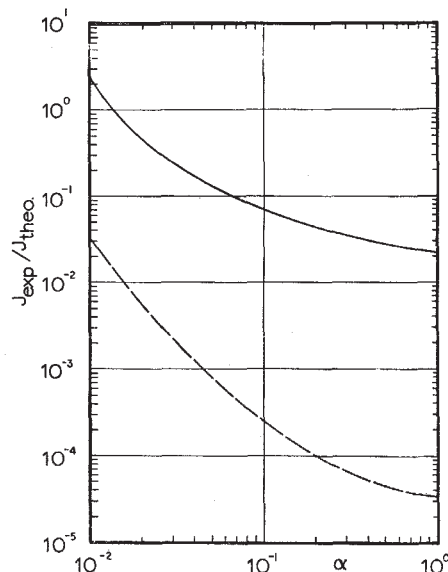
Nucleation in Steam Nozzle Condensation

THE problem of calculating the nucleation rate for condensing water vapour in the flow through a nozzle has attracted attention for at least half a century. In the 1940s, the rapid growth of interest in supersonic aerodynamics and the widespread development of supersonic tunnels led to a renewed and vigorous attack on the problem and a workable, if not wholly satisfactory, theory for an air-water vapour mixture.

As Barschdorff *et al.* point out in next Monday's *Nature Physical Science* (December 18), that theory does not work at all well for pure steam. They describe how they retraced the steps of the classical nucleation theory, adding a correction for the lack of thermal equilibrium between embryonic droplets and the surrounding vapour, and leaving as disposable constants the surface tension in the droplet and the accommodation coefficient for the condensation of water molecules. Assuming a value for the surface tension (equal to the bulk surface tension) they calculate the nucleation rate, under certain conditions, for a range of values of the accommodation coefficient (α), and compare the results with those of the experiments.

An example of such a comparison is shown in the diagram. In particular, the consequence of allowing for depar-

tures from thermal equilibrium is evident from a comparison between the chain line and the full line. That is the chief, and important, conclusion to be drawn from the communication. At the same time, it points the way to a rational analysis of experimental data which will, in time, lead to acceptable values for the accommodation coefficient.



—, Non-isothermal nucleation theory;
---, isothermal nucleation theory.

this meeting is that quantizing the gravitational field is a task which is being actively tackled in many ways.

CONTINENTAL DRIFT

Pre-Permian Probing

from our Structural Geology Correspondent
FOR how long have the continents been drifting across the Earth's surface? This is a question that has received considerable attention recently in the light of the impressive evidence of seafloor spreading and the resultant hypothesis of plate tectonics. Yet by the very nature of this hypothesis the present oceanic crust is nowhere older than Permian and hence less direct proof of pre-Permian continental drift must be sought within the continents. Many geologists have postulated large spreading oceans, with later closing episodes, to account for individual pre-Permian orogenic belts. In most cases the evidence for an ocean more than 1,000 km wide has been non-existent.

Two recent reports have examined critically the evidence for an extensive ocean accompanying the Lower Palaeozoic Appalachian/Caledonian orogenic belt. Chidester and Cady (*Nature Physical Science*, **240**, 27; 1972) have reviewed the origin and emplacement of Alpine-type ultramafic rocks with particular reference to the Appalachian system, and they recognize two genetically similar but environmentally different groups—first, those generated beneath an oceanic (sialic) crust, and, second, those generated beneath a continental (sialic) crust.

The second group is represented by Alpine-type ultramafic plutons intruded into eugeosynclinal meta-sediments, which, in many instances, can be shown to rest on a basement of continental crust. They place most of the ultramafic plutons within the Appalachians south of Newfoundland in this group, thus suggesting an origin at rifts within the mantle beneath sialic crust. There is no evidence within this part of the Appalachian belt for the former presence of oceanic crust. In Newfoundland, however, they recognize examples of their first category of ultramafic rocks—sheet-like masses analogous to ophiolite complexes of oceanic lithosphere obducted later than the Permian. They conclude that the oceanic area associated with the Appalachian/Caledonian orogen was limited to a narrow zone over Newfoundland.

Williams and Malpas (*Canad. J. Earth Sci.*, **9**, 1216; 1972) take the story a stage further by studying a section of this overthrust Lower Palaeozoic oceanic lithosphere in Western Newfoundland. Here they recognize a typical ophiolite complex with basal ultramafic rocks overlain by gabbros with an upper zone

invaded by sheeted dykes acting as feeders to overlying pillow lavas capped by pelagic sediments. Williams and Malpas confidently ascribe this ophiolite to a proto-Atlantic oceanic crust. Although the underlying thrust plate contains sheeted dykes feeding pillow lavas thought to be consanguineous with those in the overlying plate, it also includes fragments of metamorphosed granitic rock which would seem to represent incorporated older continental crust within the spreading early Palaeozoic ocean. Williams and Malpas use this argument to suggest that the early Palaeozoic ocean was a small ocean basin that still contained older remnants which were not swept away by the extensive spreading prerequisite to wide ocean spreading.

These two lines of approach suggest that at least the oceanic spreading within the Caledonian/Appalachian belt was minimal. A more general approach to the problem is presented by Engel and Kelm (*Bull. Geol. Soc. Amer.*, **83**, 2325;

1972), who compare and contrast the structural and petrological developments of Archaean orogenic belts with those of post-Permian age. They find that, although the Archaean belts in common with post-Permian belts contain abundant ultramafic rocks, their presence is attributable to a thin sialic crust, through which the mantle rocks can readily penetrate, rather than to the extensive seafloor spreading with marginal obduction so characteristic of the post-Permian belts. They contrast the long narrow zones of post-Permian orogenesis with the continent-wide Archaean belts and suggest for the latter a series of island arcs appressed onto intervening narrow zones of thin sialic crust with insignificant crustal drift. The apparent continuity of Archaean structures across younger, pre-Permian orogenic belts suggests that these, too, are associated with only minor continental drift.

Although Engel and Kelm are forced to seek a mechanism in mantle convec-

Structure of the Oslo Graben

THE Oslo Graben in Norway, an area about 40 km wide and 220 km long, subsided into the surrounding Precambrian shield accompanied by magmatic and tectonic activity during the Lower Permian. Because it represents a site of ancient rifting, its characteristics are clearly of particular interest not only in their own right but also in comparison with modern active rift systems. As a first step in the comparative process, I. B. Ramberg has attempted a crustal structure determination of the graben on the basis of the more than 3,000 gravity observations made there since 1966, the results of which he presents in next Monday's *Nature Physical Science* (December 18).

The overall Bouguer anomaly along the graben turns out to be positive, although superimposed upon it are smaller minima, which correlate with exposed granitic and syenitic intrusions. Outside the graben the Bouguer gravity values correlate negatively with topography. Within the graben area, however, this correlation breaks down, thus suggesting (and confirming the seismological evidence) that the graben has a different structure from its surroundings.

Gravity anomalies alone are never, of course, capable of giving a unique structural interpretation, and so Ramberg has produced three models using seismic and geological controls. The first assumes that the smoothed gravity profile (total profile minus local geological effects) arises solely from variations in the depth of the Moho; and on this basis a considerable thinning of the crust below the graben is indicated. The second model, which

takes density variation into account, suggests that the positive Bouguer anomaly must, in part, be due to a positive density contrast within the crust at intermediate to deep levels. The third model tries to accommodate a mass excess high in the crust, but is considered by Ramberg to be an unlikely solution on geophysical grounds. Ramberg then goes on to consider the first two models in the light of the geology and petrology of the area, concluding that the second (thinner crust plus higher density at depth) accords better with the available evidence.

To explain the results in physical terms, Ramberg suggests that plastic deformation occurred in the deeper crust, accompanied by the rise of heavy mantle material from below, whereas in the brittle upper crust the deformation led to fracturing. The presence of normal block faulting, dilatational dykes and igneous intrusions of mantle origin in the upper crust is consistent with current views of both oceanic and continental rifts. But there is an important seismological difference between the graben and modern rifts in that the anomalously low P wave velocities observed below the rifts are not obtained below the graben—on the contrary, the graben gives clear Moho refractions with normal upper mantle velocities.

Ramberg's explanation for this difference, assuming the graben and modern rifts to be the products of similar deep-seated processes, depends on the fact that the thermal régime associated with rifting no longer applies to the graben but the physical consequences do.

tion to account for the evolutionary growth in lithospheric spreading that they envisage, its precise nature is not as yet clear.

RARE EARTHS

A New Interaction

from a Correspondent

EXPERIMENTAL studies by Liu of the magnon and phonon spectra of the heavy rare earth metals terbium and dysprosium have led to the prediction of a novel magneto-elastic interaction in these materials (*Phys. Rev. Lett.*, **29**, 793; 1972). Tb and Dy crystallize in the hexagonal close packed (h.c.p.) structure and are ferromagnetic below 218 K and 79 K respectively; in this regime the magnetic moments are confined to the hexagonal planes. The characteristic magnetic properties of these materials are, of course, determined by their electron configurations, and, proceeding through the rare earth series, the 4f shell is being filled but is always surrounded by two electrons in the 5s shell, six in the 5p shell and two in the 6s shell. In the metal three of these electrons are lost to the conduction band leaving the remainder screening the 4f shell of a particular ion from its neighbours. This screening ensures that the orbital motion of the 4f electrons as well as their spin motion contributes to the resultant ionic moment; spin-orbit coupling provides the interaction between the orbital magnetic moment and the spin moment. The individual ionic moments are coupled indirectly (through the conduction electrons) by the Ruderman-Kittel interaction, which produces the magnetic order.

The most powerful experimental technique for studying elementary excitations in these materials is the scattering of incident neutrons. Measurement of the frequency shifts of inelastically scattered neutrons enables the energy-wavelength spectra (or, more usually, the energy-reciprocal wavelength (k) spectra) of phonons, the elementary quanta of lattice vibrations, and magnons, the elementary quanta of magnetic spin vibrations, to be determined in different crystalline directions. Studies of the magnon and phonon spectra of Tb along the hexagonal (c) axis at 79 K using inelastic scattering of neutrons (*Inter. J. Magn.*, **1**, 271; 1971) reveal two specific cases of mode mixing where, instead of the magnon and phonon modes simply crossing over in reciprocal (k) space, they mix with one another.

The mixing at low values of k between transverse acoustic phonons (TA) and acoustic magnons (MA) can be satisfactorily explained in terms of conventional magnetostriuctive interactions; symmetry requirements do not, however, allow a similar explanation for the

second mixing found at higher k between transverse optic phonons (TO) and MA. The symmetry argument goes briefly as follows: the h.c.p. structure is composed of two interpenetrating hexagonal sub-lattices and the TA and TO modes result from the vibration of the two sub-lattices in phase and 180° out of phase respectively. The magnetization fluctuations of the MA correspond to those of the TA and hence the two modes can mix. For MA to mix with TO, however, the symmetry or "double-zone" representation must be broken.

Liu has postulated that the symmetry breaking mechanism, described by Herring in 1937 (*Phys. Rev.* **52**, 361) in a study of the electron bands of h.c.p. metals, is responsible for this unexpected mode mixing. This mechanism is the spin-orbit coupling that produces the magnetic moments in the first place. Calculations of the band structure of heavy rare earths have already shown that spin-orbit coupling can cause the double zone representation to be broken. The method of mixing proposed by Liu depends upon there being some interaction between the spin-orbit coupling

and the conduction electrons. An incoming phonon may be absorbed by the conduction electrons producing an electron-hole pair both of the same spin; a magnon may break up into an electron-hole pair but this time with opposite spins. The only way these two modes can mix within this mechanism is for spin-orbit coupling to produce a spin-flip in one of the modes, whereupon a phonon can turn into a magnon or *vice versa*.

In the rare earths the spin orbit coupling is screened from the conduction electrons by the 5s and 5p electrons, and if Liu's mechanism is the correct one then this mode mixing is the first experimental evidence for an interaction between the spin orbit coupling and the conduction electrons. Liu supports his case by calculating the energy splitting (Δ) caused by the mode mixing and obtains a very reasonable agreement with the experimental value, especially in view of the unexpectedly large size of Δ . Finally Liu's mechanism also explains the insensitivity of Δ to temperature, which is in contrast to the strongly temperature-dependent energy splitting observed between TA and MA.

More Red Sea Brine Pools

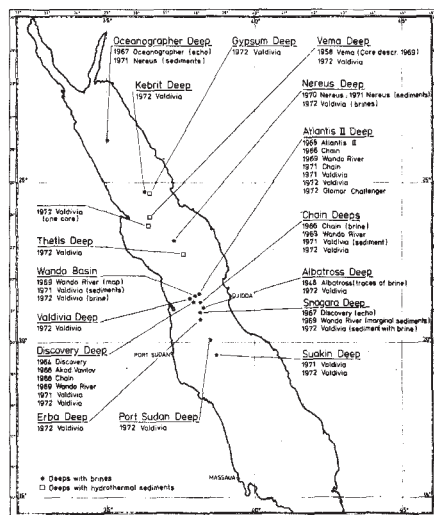
HOT brine pools associated with metaliferous sediments in the Red Sea have been known since 1964, although traces of brine were discovered in the Albatross Deep as early as 1948. The result of the first detailed studies carried out between 1964 and 1966 was the description of three brine pools (Atlantis II Deep, Discovery Deep and the Chain Deeps) offshore from Djidda and close together on the Red Sea's central rift zone. With one (unpublished) exception, however, there have been no discoveries of brine pools outside the area of the Atlantis II Deep since then.

But in next Monday's *Nature Physical Science* (December 18) Bäckér and Schoell transform the picture completely by reporting no less than thirteen new brine pools and several areas of sediment of hydrothermal origin along the central rift zone (see figure). These discoveries were made during three cruises which surveyed the whole central rift from the Subair Islands to Abukizaan.

An important point to emerge from the new surveys is that some of the brine pools differ both physically and chemically from that of the well-known Atlantis II Deep. In general, the deeps contain zones of differing salt concentration, the lowest layer being the most concentrated. There are, however, differences in the transition zones of the deeps (the zones of mixing between the brines and the overlying sea water). For the Atlantis II Deep, the deeps close to it and one or two other deeps, the transition zone is characteristically layered

itself, the layering being caused by stepwise variations of temperature and chlorinity. But in other cases small undifferentiated transition zones are observed.

Chemically, the Atlantis II Deep and neighbouring deeps have the highest chlorinities. Moreover, the depletion of Mg and SO_4 associated with Atlantis II and its neighbours is not observed elsewhere. Finally, chemical and physical characteristics seem to be similar for deeps within the same area, which implies subsurface connexions between the deeps in any particular group.



Distribution of brine pools and brine-derived sediments in the Red Sea (principal investigations up to May 1972).

Shift Reagents in NMR Spectroscopy

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Much more information can be extracted from nuclear magnetic resonance spectra of complex molecules if shift reagents are used to separate resonances that would otherwise overlap.

THE essence of the n.m.r. (nuclear magnetic resonance) experiment is observation of transitions between nuclear spin states in a magnetic field through the absorption of radio-frequency power. The exact absorption frequency of a nucleus in an organic molecule is characteristic of its local electronic environment because this generates a small magnetic field to accompany the principal applied field. The observed resonant frequency variations, called chemical shifts, commonly extend over only about 10 parts per million (p.p.m.) of the applied field for protons, and some 200 p.p.m. for ^{13}C , although they can be more substantial for other nuclei (see, for example, ref. 1). The proton n.m.r. spectra of very simple molecules are frequently readily analysed because the resonances do not overlap at easily accessible field strengths (a magnetic field of 23 kgauss gives proton resonance at 100 MHz), but in complex molecules many resonances overlap and important structural information is lost. The power and limitations of n.m.r. are illustrated in Fig. 1, which shows that some useful resonances (especially the sharp singlets of the methyls) are resolved, but that most of the absorption is in the form of an ill-defined "methylene envelope" ($\delta=1$ to 3 p.p.m.) at 60 MHz. The various resonances shifted from the envelope are due to protons adjacent to the functional groups. The signal at 4.91 δ , which is caused by the CH_2 group in the lactone ring, is not well resolved at 60 MHz, but at 100 MHz (Fig. 1, insert) it gives a clear four line pattern (AB). The splittings of the signals are the consequence of couplings between adjacent protons and the magnitudes of such coupling constants are very important for determination of

structures^{1,2}. The methylene envelope is hardly improved at 100 MHz.

Recently, large expenditures of finance and manpower have been directed to the development of superconducting magnet instruments operating at 200 to 300 MHz, and although these are very useful because of their greater sensitivity, the approach does relatively little to improve the proton magnetic resonance technique.

The effects in n.m.r. of paramagnetic ions have long been recognized^{3,4} and have been brilliantly exploited in studies of compounds such as that shown in Fig. 2a: unpaired electron density from the metal ion is transmitted through the π system to cause very large "contact" shifts in both ^1H and ^{13}C spectra^{5,6}, the shifts being related to the unpaired electron density at the nuclei. Such results are, however, only obtainable in very favourable cases, and are of little general applicability, for they rely on the preparation of actual complexes. Attempts to use reversible coordination to Co^{2+} compounds to simplify spectra have also been reported^{7,8}, but the real breakthrough came in 1969 when Hinckley⁹ discovered that the addition of the pyridine adduct of $\text{Eu}(\text{DPM})_3$ (Fig. 2b) to a carbon tetrachloride solution of cholesterol caused important selective downfield shifts in the spectrum of the steroid without serious line broadening. For obvious reasons, the europium complex was named a shift reagent.

Implicit in Hinckley's discovery were the possibilities of useful spectral simplification by removal of signal coincidence and the characterization of a nucleus not only in terms of its local environment but also by its geometrical relationship with respect to one or more distant functional groups (see later). We reasoned that the pyridine-free complex should be a superior shift reagent, the pyridine being a competitive inhibitor for association with the substrate, and we indeed found that the absence of pyridine increased the shifts in cholesterol by a factor of four¹⁰.

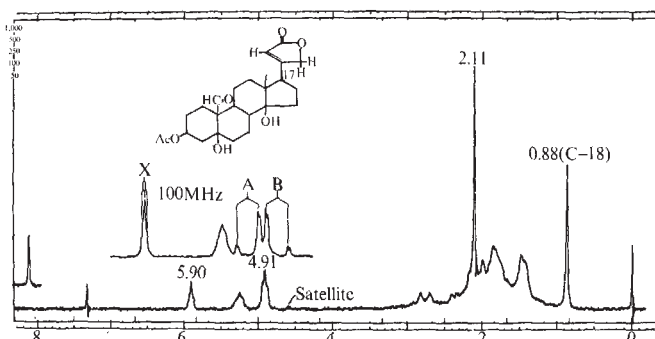


Fig. 1 60 MHz ^1H n.m.r. spectrum of acetyl strophantidin in CDCl_3 solution. From page 45 of ref. 2. δ values are the shifts in p.p.m. from the inert standard tetramethylsilane $(\text{CH}_3)_4\text{Si}$.

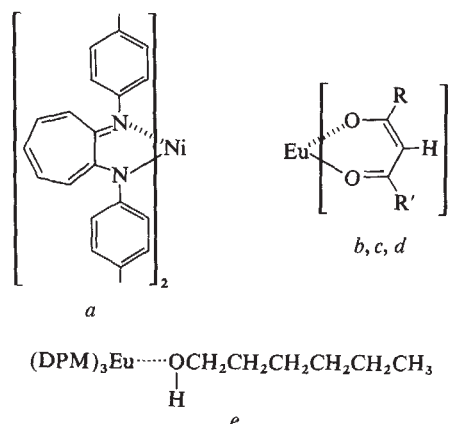


Fig. 2 a, A compound studied by exploiting the effects of paramagnetic ions in n.m.r.; b, $\text{R}=\text{R}'=\text{t-butyl}$; c, $\text{R}=\text{t-butyl}$, $\text{R}'=\text{CF}_2\text{CF}_2\text{CF}_3$; d, $\text{R}=\text{t-butyl}$, $\text{R}'=\text{CF}_3$; e, association of the europium complex with the substrate being studied.

Table 1 Some Typical $(\text{EuDPM})_3$ -induced G Values for Substrates in CCl_4 Solution*

Functionality	G (p.p.m.)	Substrate concentration	Reference
RCH_2NH_2	150	0.2 M	11
RCH_2OH	100	0.2 M	11
RCH_2NH_2	35	0.2 M	11
RCH_2OH	25	0.2 M	11
$\text{Me}_2\text{N.CO.H}$	34	7%	14
$\text{Me}_2\text{N.CO.Me}$	12.5	7%	14
RCO.H	19	0.2 M	11
$(\text{RCH}_2)_2\text{CO}$	11	0.2 M	11
$(\text{RCH}_2)_2\text{O}$	10	0.2 M	11
RCOOMe	14†	0.2 M	11
RCH_2COOMe	13†	0.2 M	11
Me_2SO	8.9	0.1 M	15
$(\text{RCH}_2\text{O})_3\text{PO}$	8.8	7%	14
$(\text{RO})_2\text{PO.Me}$	7	0.2 M	16
RCH_2CN	5	0.2 M	11
RCH_2S	<1	0.2 M	11, 19
RCH_2OX	<1	0.2 M	19 and unpublished observations made in this laboratory
(X is CPh_3 , COCF_3 or tosyl)			

* The relevant protons are underlined in the structural formulae.

† The figures for this functional group presented in ref. 11 were in error by a factor of two.

The great power of $\text{Eu}(\text{DPM})_3$ is illustrated in Fig. 3 which shows the 100 MHz proton spectrum of n-hexanol in the absence and presence of shift reagent: the featureless bands at values of δ between 1.2 and 1.7 in Fig. 3a are readily modified to yield the first order spectrum (Fig. 3b) with the expected multiplicities, although the hydroxyl resonance is shifted too far to be recorded¹⁰. Similarly, the five-proton aromatic singlet of benzyl alcohol can be made first order¹⁰, as can the otherwise uninformative spectra of quinoline¹¹, dimethyl tetradecandioate [$\text{MeO.O}(\text{CH}_2)_{12}\text{COOMe}$] (ref. 11), 4-t-butylcyclohexanols¹²,

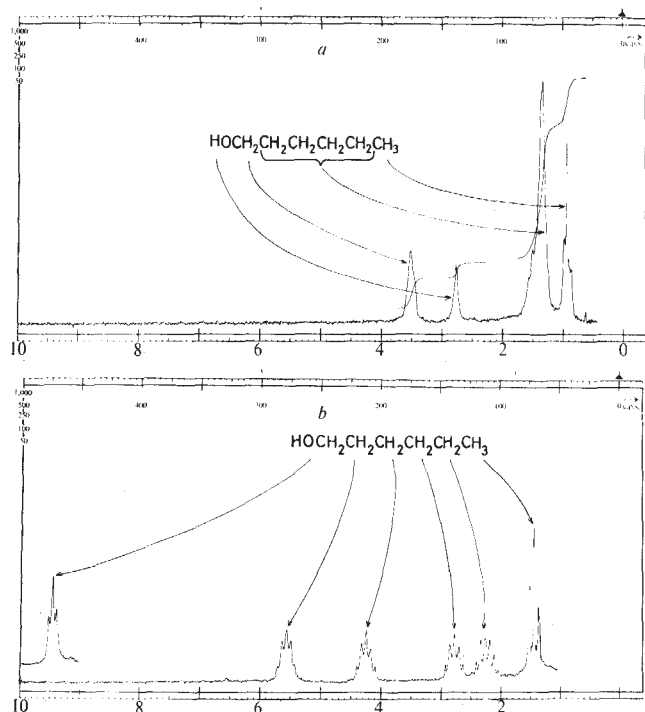


Fig. 3 a, 100 MHz ^1H n.m.r. spectrum of n-hexanol in CCl_4 solution; b, the same solution after the addition of 0.29 molar equivalents of $\text{Eu}(\text{DPM})_3$.

and many other compounds. Without $\text{Eu}(\text{DPM})_3$ such compounds would yield these valuable first order spectra only in extremely high field spectrometers requiring magnet technology which is quite unattainable at present. Fig. 2e shows schematically how the europium complex associates with the substrate being studied (n-hexanol, for example) at its polar functional group. In the simplest terms, the europium provides a local magnetic field which falls off as the inverse cube of the distance from the europium atom, and thus spreads out the spectrum.

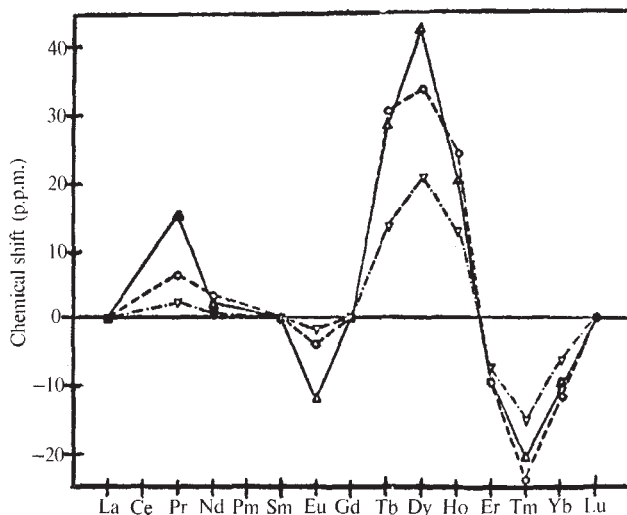
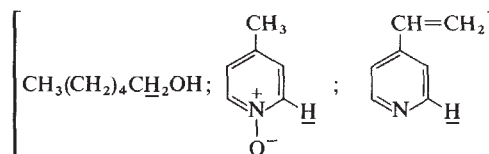


Fig. 4 Induced shifts for ^1H resonances (see underlined protons) of n-hexanol (Δ), 4-picoline-N-oxide (∇), and 4-vinylpyridine ($\circ$) (each 0.8 M in CDCl_3) in the presence of 0.1 M $\text{Ln}(\text{DPM})_3$ (ref. 24).



Good straight lines are obtained when the induced shift for a given proton is plotted against molar ratio M ($M = [\text{Eu}(\text{DPM})_3]/[\text{substrate}]$) in the range $0.1 < M < 0.8$. At low values of M residual moisture can interfere¹¹⁻¹³, and at high values the substrate begins to become saturated with shift reagent. The gradients (G) of the straight line sections are roughly characteristic for any proton in a given relatively unhindered environment; Table 1 shows some typical values of G (in p.p.m. per mol $\text{Eu}(\text{DPM})_3$ per mol substrate) for substrates dissolved in CCl_4 . Shifts are similar in CS_2 and d_6 -benzene, but somewhat smaller in CDCl_3 (ref. 11). They also decrease on dilution^{11,13,15}.

Clearly there is at least a qualitative correlation between values of G and the substrate basicity, and a quantitative relationship has been established for some p-substituted anilines (ref. 17, but see ref. 18). This fact has been used to "turn off" selectively various functionalities in a steroid by derivatization¹⁹. The derivatization also takes advantage of the fact that $\text{Eu}(\text{DPM})_3$ is a "hard" Lewis acid²⁰, and is virtually inert to second row bases such as S and P. $\text{Eu}(\text{FOD})_3$ (Fig. 2c) has been recently described as a "vastly superior" shift reagent because of its greater solubility and Lewis acidity²¹, and although this is undoubtedly true for weakly binding substrates (esters and below, see Table 1) or for substrates completely inert to $\text{Eu}(\text{DPM})_3$ such as halides and metal carbonyls²², it is not the case for highly basic substrates because of the occurrence of several anomalies which will be discussed later.

The DPM complexes of all the other lanthanides have also been evaluated as shift reagents^{23,24} and a summary of their

shift powers is shown in Fig. 4. It should be noted, however, that the heavier lanthanides also cause severe line broadening, precluding their use in work where the spin coupling information is valuable. The best available upfield shifting complex is $\text{Pr}(\text{DPM})_3$, which broadens lines only slightly more than $\text{Eu}(\text{DPM})_3$ (ref. 24). For mono-functional substrates the ratios of shifts induced by the various DPM complexes are substantially the same*, but large variations are seen in some polyfunctional substrates where chelation can occur and therefore where the ionic radius of the metal is more critical

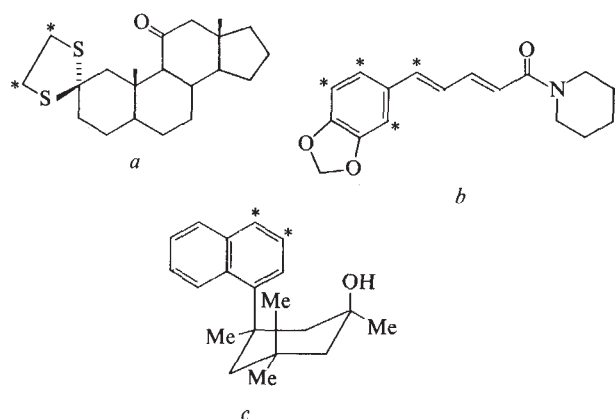


Fig. 5 Three compounds in which the protons marked by an asterisk exhibit a shift reversal.

(refs. 25 and 26, and our unpublished observations). More results in this area would usefully clarify the present confused situation.

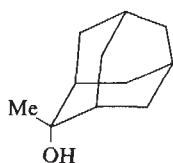
Mechanism of the Shifts

It now seems clear that the observed shifts (ΔH) are dominated, in the case of σ frameworks, by the pseudocontact interaction, that is a magnetic field effect acting through space rather than an effect through bonds. Equation 1 is valid for axially symmetric molecules⁵; R is the nucleus-metal distance vector, and ϕ is the angle between that vector and the principal symmetry axis. This axis is usually taken to be

$$\Delta H = C \cdot \frac{3 \cos^2 \phi - 1}{R^3} \quad (1)$$

the line connecting the metal ion and the coordinating atom so that ϕ is the H-Eu-O angle for the protons in an alcohol. C is a constant for any given metal adduct at a given temperature, and is dependent on the magnetic anisotropy of the ion²⁷. As C is the same for all nuclei in a molecule, the shift ratios in that molecule are dependent only on molecular geometry, in sharp contrast to the contact shifts seen in the compound

Fig. 6 2-Methyladamantan-2-ol.



* We are unable to reproduce the n-hexanol anomalies of Pr and Eu reported by Horrocks and Sipe²⁴.

in Fig. 2a. The shift reagent, therefore, is merely a means of bringing a substrate under the influence of a strong local magnetic field.

Evidence that it is indeed the pseudocontact shift that is observed is provided by the large number of excellent correlations which now exist between ^{13}C or ^1H shifts and chemically reasonable coordination and substrate geometries^{9,11,12,24,28-32}. Although power dependences of R other than three also apparently give good fits to the experimental data³³, this can only be regarded as a consequence of inadequately precise experimental data, or incorrect placing of the metal ion during calculation (see ref. 33 and section VIII of ref. 11 for further details). The only general exceptions to the rule of pseudocontact shifts for protons and ^{13}C seem to be for the carbon bonded to the coordinating atom, where the shifts are not always as predicted^{28,34} and therefore where contact shifts must be invoked. The shifts in ^{14}N spectra induced by shift reagents are, however, almost exclusively contact in nature^{13,35} and aquo-lanthanide ions induce large contact shifts for the cases of both ^{31}P and ^{13}C in phosphates and carboxylate, respectively (refs. 13 and 36, and our unpublished observations). In addition, a definite case of the transmission of contact shifts from $\text{Eu}(\text{FOD})_3$ through the π system of pyridine-N-oxide has been observed in this laboratory (P. McArdle, personal communication); such effects may be common when a π -system extends from the site of coordination.

These exceptions apart, the pseudocontact nature of the shifts seems well established and may therefore be employed in structural studies. Frequently, the "distance only" criterion may be used, that is, R^{-3} alone. But, as has been pointed out^{13,28}, it must be used with care because the sign of $3 \cos^2 \phi - 1$ changes when $\phi > 54.7^\circ$ and, therefore, upfield shifts should be seen for nuclei in these positions. This shift reversal has been observed for protons in several cases in which the substrate envelops the metal ion—for example for those protons marked by an asterisk in the compounds shown in Fig. 5.

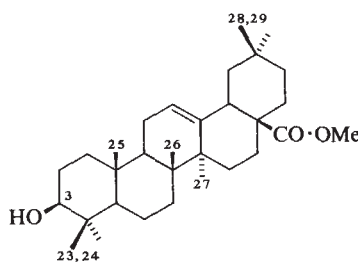
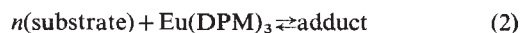


Fig. 7 Methyl oleanolate.

Coordination occurs at the amide carbonyl in the compound shown in Fig. 5b.

Nature of the Interactions

The spectra observed are clearly averages of the spectra in the free and bound states because of fast exchange, and it is now well established that the value of n in equation 2 is 1 (refs. 13, 38 and 39, and J. Reuben, personal communication).



The value of K , the association equilibrium constant, has been estimated to be as low as 12 l. mol^{-1} for primary alcohols³⁸, but we have shown¹³ that such a small value could not lead to the well documented and very sharp limit in shift at values of M approaching unity (refs. 13, 34, 39 and 40, and J. Reuben, personal communication). We have determined K for

2-methyladamantan-2-ol (Fig. 6) to be 250 ± 50 , with a limiting shift for the methyl group of 19.0 ± 0.5 p.p.m., and similar values have been reported for pyridine (ref. 39, and J. Reuben, personal communication). For most substrates, $100 < K < 1,000$ (ref. 13).

By contrast with this simple picture, $\text{Eu}(\text{FOD})_3$ (Fig. 2c) and its analogue, $\text{Eu}(\text{PTA})_3$ (Fig. 2d), seem to change the stoichiometry of their adducts with molar ratio, for strongly basic substrates at least^{13,41}. This makes interpretation of the data very difficult, for the proton shift ratios are dependent on the concentration of shift reagent. Indeed, in amines, some resonances shift upfield after a movement of 20 p.p.m. downfield. This is the chief drawback associated with fluorinated shift reagents and should be borne in mind whenever they are used.

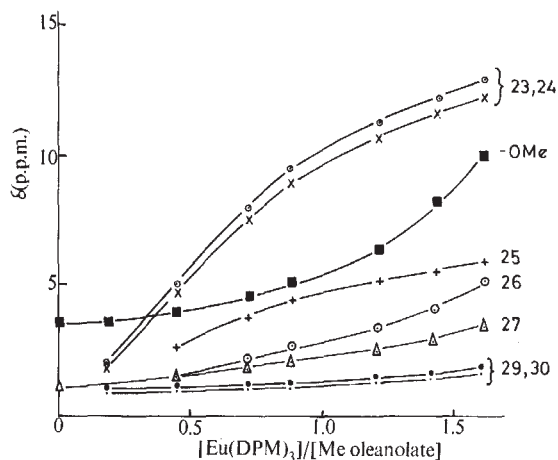


Fig. 8 The effect of added $\text{Eu}(\text{DPM})_3$ on the methyl resonances of methyl oleanolate (Fig. 7) (approximately 0.09 M in CCl_4 solution).

Generalization of the mathematical analysis to a set, j , of x functional groups each with an independent equilibrium constant, K_j , and concentration, S_j , is a relatively simple matter¹³. For example, it yields equation 3 for the initial shift gradient $[G(H_k)_i]$ of the k th proton of the i th substrate of the mixture. Applications of equation 3 include determination of equilibrium constants¹³ and others to be described later.

$$G(H_k)_i = \Delta_{1im}(H_k)_i \cdot \frac{K_i S_i}{1 + \sum_{j=1}^x K_j S_j} \quad (3)$$

Detailed calculations¹³ for bifunctional compounds such as methyl oleanolate (Fig. 7) predict that at low concentrations of the shift reagent, coordination should occur chiefly at the 3β -hydroxyl group, but that as the $\text{Eu}(\text{DPM})_3$ concentration is increased, relatively more coordination should occur at the

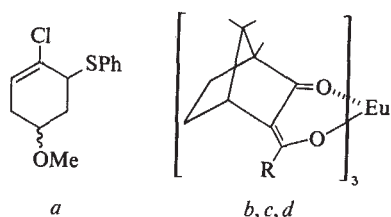


Fig. 9 a, A compound whose stereoisomers illustrate the simplest level of mixture analysis; b, $\text{R} = \text{CF}_3$; c, $\text{R} = \text{CF}_2\text{CF}_2$; d, $\text{R} = \text{fenchyl}$.

ester function. The striking confirmation of these predictions is shown in Fig. 8, and the same effect has been clearly seen in the compound³⁴ shown in Fig. 5b and other cases^{42,43}.

An efficient graphical method for separating the contributions of the two functional groups to observed shifts has been described by Hinckley *et al.*⁴⁴, but it is at present restricted to substrates for which the functional groups are spatially well separated.

Applications

There are obviously many potential uses for shift reagents in chemistry, and this has undoubtedly been one of the chief driving forces behind the enormous volume of published material in this field. It now seems clear that n.m.r. applications of shift reagents fall into three principal classes, although these are somewhat interdependent. First, there are methods based on competition experiments; second, there is the use of expanded spectra to obtain general structural information and, third, there is the use of relative shifts to obtain distance information. We shall describe here an illustrative set of applications, rather than an exhaustive one. In addition, circular dichroism effects with α -glycols induced by $\text{Pr}(\text{DPM})_3$ have been applied in assignments of configurations^{45,46}.

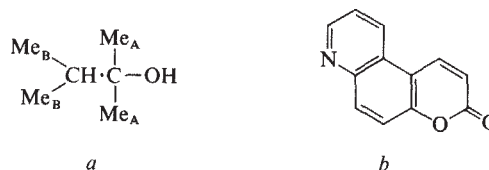


Fig. 10 Compounds discussed in the text.

The simplest level of mixture analysis is illustrated by the diastereoisomers of Fig. 9a (unpublished observations made in our laboratory). These compounds are not readily separable but for the purposes of mechanistic studies (ref. 47 and further details to be published) it was necessary to know their relative proportions. Their normal spectra are super-imposable at 100 MHz but the diastereoisomers have different affinities for $\text{Eu}(\text{DPM})_3$ and the methyl resonances are shifted to different extents, enabling assessment of relative proportions from signal intensities. Similar results have been obtained for other classes of compounds⁴⁸⁻⁵⁰.

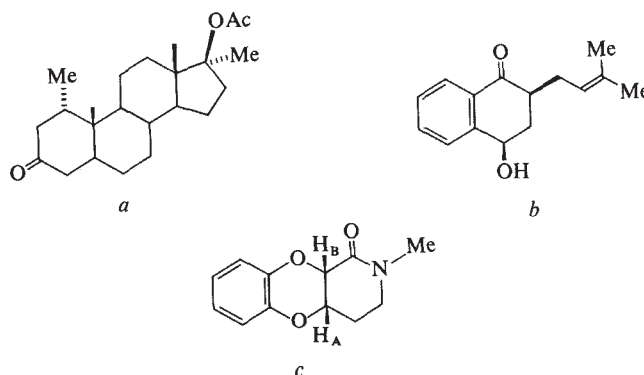


Fig. 11 Compounds discussed in the text. a, Ref. 58; b, ref. 59; c, ref. 62.

More important, the diastereoisomeric adducts formed between optically active substrates and the chelates shown in Fig. 9a, b and c have different stabilities⁵¹⁻⁵³. The resonances of the enantiomers of the substrates are therefore shifted to

different extents, enabling the optical purity of the substrate to be readily measured. The complexes shown in Fig. 9b, c and d achieve this resolution with many substrates but with varying efficiencies; no rationale of these variations is yet available. Changes in the shift ratio analogous to those of $\text{Eu}(\text{FOD})_3$ have been reported for the complex shown in Fig. 9c.

Equation 3 could be used to make a quantitative assessment of the discrimination of Fig. 8b, c and d for enantiomers, or indeed any similar effect. As we have shown elsewhere⁵⁴, relative equilibrium constants in a mixture can be determined with a precision of about 0.1% in K_A/K_B , providing unprecedented detail in such studies. It is, for example, readily shown by use of $\text{Eu}(\text{DPM})_3$ in n.m.r. competition experiments that deuterium is more electropositive than protium, and that replacement of protium by deuterium in methyl A of Fig. 10a increases the stability of the $\text{Eu}(\text{DPM})_3$ adduct by $3.45 (\pm 0.21)$ calorie mol^{-1} deuterium, whereas substitution in methyl B gives only a stabilization of $0.75 (\pm 0.08)$ calorie mol^{-1} deuterium⁵⁴. These measured differences (in free energies of association of the order of 3 kcalorie mol^{-1}) demonstrate the power of the method.

Spectra expanded by $\text{Eu}(\text{DPM})_3$ can frequently be used without reference to any assumptions about shift mechanism or adduct stoichiometry. Thus, deuterium substituted remotely from a functional group may be assayed, even though in the unshifted spectrum the corresponding proton resonance is obscured^{55,56}. Similarly, a product from a synthesis was shown

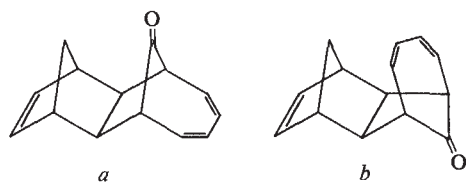


Fig. 12 Two structures with different shift patterns.

to be Fig. 10b (rather than a linear possibility) from the multiplicities revealed by $\text{Eu}(\text{DPM})_3$ (ref. 57), and the stereochemistries of many compounds such as Fig. 11a and b have been determined solely from the coupling constants revealed⁵⁸⁻⁶². Care must, however, be exercised in the interpretation of such data, because addition of $\text{Eu}(\text{FOD})_3$ to the compound shown in Fig. 11c causes J_{AB} to vary from 3 to 8 Hz, presumably by changing the ring conformation⁶². Where necessary, the magnitude of the couplings should be monitored over a range of concentrations of the shift reagent, and extrapolated to zero concentration, or, if possible, the parameters derived from the shift data should be used to calculate the appearance of the unshifted spectrum and this should be compared with the actual original⁶³. Applications of this type are many but unremarkable.

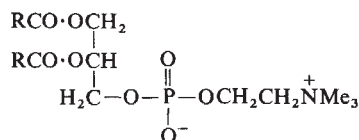


Fig. 13 Lecithin.

The most important impact of shift reagents in chemistry and biology is a result of the apparent validity of the pseudocontact shift equation, which allows geometrical relationships within the substrate molecule to be determined. There is, however, an important proviso, namely that analysis of shift data will yield the shape of the substrate in its bound form. Except for the case of rigid substrates such as steroids, the

bound conformation need not necessarily be the same as that of the free solution form, and neither of these is necessarily the biologically active conformation. Indeed, not only has a case of changed couplings been recorded⁶², but also changes in mobile isomer populations^{64,65}.

The correlation of shift data with R^{-3} alone, neglecting angular variables, has been used to distinguish between possible structures which would have very different shift patterns, for example, Fig. 2a and b (ref. 66). This type of application, which seems justified in such clear cut cases, is very popular in structural and conformation studies⁶⁶⁻⁷² and in the assignment of proton resonances^{40,73,74}. Where inspection of molecular models reveals that variations in ϕ are likely to be significant in determining shifts, the $(3 \cos^2 \phi - 1)$ terms should also be included. The great power of the pseudocontact shift equation is illustrated by the assignment of ^{13}C spectra of borneol and iso-borneol from the observed shifts^{27,28}, and should be increased further when ^{13}C data can be correlated by computer with chemically reasonable bond lengths and angles to yield an analytical method for structural determinations (unpublished observations made in this laboratory). The latter approach would be in contrast to the existing methods described above, which merely take the best fit of various offered solutions, and when suitably developed could conceivably offer competition to X-ray crystallography as a powerful method of structural determination. A further possible use of lanthanide ions in ^{13}C spectra is in the enhancement of signal intensity by shortening relaxation times (unpublished observations made in this laboratory).

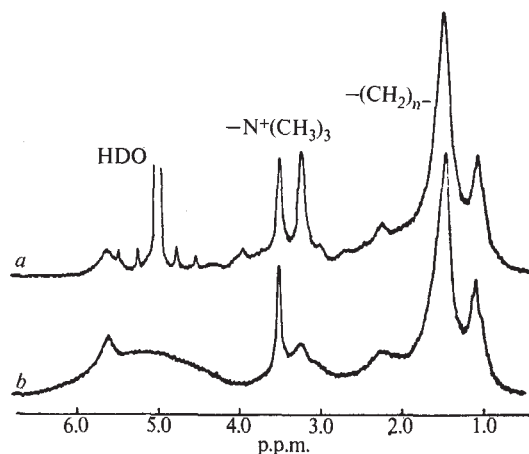


Fig. 14 ^1H n.m.r. spectra of a 5% w/v dispersion of egg yolk lecithin in D_2O . a, After addition of 2×10^{-2} M/l $\text{Eu}(\text{NO}_3)_3$; b, after addition to sample A of 3×10^{-3} M/l MnSO_4 . From page 346 of ref. 81.

Implications for Biology

The development of the use of $\text{Eu}(\text{DPM})_3$ and its analogues in non-polar solvents has been accompanied by investigations in polar and aqueous systems. Coordination only occurs at very basic functional groups such as phosphates and phosphonates^{13,36,65,75}, carboxylates^{13,76,77}, and the oxides of amines, phosphines and arsines¹³. Applications are therefore limited in organic chemistry^{13,77}, but are much more important in biological systems, for lanthanide ions can frequently substitute for Ca^{2+} and Mg^{2+} while retaining biological activity^{78,79}. There is thus the possibility of investigating the shapes and sizes of active sites. As with $\text{Eu}(\text{DPM})_3$, studies have so far demonstrated possibilities rather than solutions to many problems, instructive though they may be.

The coordinated conformation of adenosine monophosphate has been determined from shifts induced by lanthanide ions together with the accompanying line broadening (which has an

isotropic R^{-6} dependence⁸⁰), and this conformation has been shown to correspond closely with that determined by X-ray crystallography⁷⁵. Similarly, the binding of lanthanides to a lysozyme-inhibitor complex corresponds closely to the solid state situation⁷⁶. Lanthanide ions have also been extensively used in the assignment of the ^{13}C spectra of AMP (ref. 65) and NAD (J. Feeney, private communication).

The interaction of paramagnetic ions with lipid bilayer membranes gives particularly dramatic and promising results⁸¹: the normal proton n.m.r. spectrum of lecithin (Fig. 13) in the form of a sonicated dispersion in D_2O shows a sharp singlet at 83.6 due to the choline NMe_3 group. Addition of Eu^{3+} causes this singlet to split into two peaks as shown in Fig. 14a. This is because the lecithin is in the form of bilayered micelles, and the added ions are able to interact only with the external surface, presumably at the phosphate group. Addition of Mn^{2+} ions to this solution broadens only the resonance shifted by Eu^{3+} (Fig. 14b), giving further proof that the inside and outside layers are not in rapid exchange with each other and that they are impermeable to metal ions. (The extensive applications of Mn^{2+} ions in enzyme studies are described by Mildvan and Cohn⁸². A general review of biological n.m.r. has been given by Jardetzky and Wade-Jardetzky⁸³.) Further studies in this field designed to elicit information on membrane permeability and structure are undoubtedly feasible and should prove most valuable.

J. K. M. S. thanks the Science Research Council for financial support.

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Properties of Photons determined by Interferometric Spectroscopy

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Black body spectroscopy has been neglected by experimentalists for fifty years. We propose to apply interferometric methods to black bodies with the prospect of getting temperature values based on frequency standards in the range from 90 K and upwards. When applied to higher temperature sources, the same methods could tell us new things about photons.

THERMODYNAMIC arguments can establish a zero of temperature and the Kelvin scale, but numbers on the scale are, at present, adopted values for identifiable phenomena such as the triple point of water¹. A consequence of the use of a material standard is that temperature values are unrelated to the mass-length-time dimensional system except by the use of Boltzmann's constant created for the purpose.

Advances in spectroscopy and numerical analysis enable us to consider measuring temperature directly in terms of frequency using black body radiation. As a working medium for thermometry, a photon gas has the advantage of behaving ideally as far as is known. This is in contrast with molecular gases whose properties have to be extrapolated to zero pressure to conform with the Kelvin scale.

Fig. 1 shows how a black body enclosure can transfer temperature information from a thermal experiment to a radiation field. If the blackness of the enclosure can be established, and if we make relative power measurements at known frequencies, a frequency-based temperature scale can be realized. One scheme locates the maximum spectral power density which Wien's Law uniquely relates to temperature. If Planck's Law correctly describes the frequency distribution of black body radiation, the whole spectrum can be used to give a temperature value and redundancy provides information about the source and measuring system.

Planck's radiation constants are the basis of present temperature values above the gold point (~1,338 K), but we believe that frequency-based values can now be extended to much lower temperatures. We show that interferometric spectroscopy with appropriate numerical analysis could give

such temperature values in the range 90 K to 1,400 K with accuracies of 0.01 K.

There are additional motivations for making new spectroscopic measurements on black body sources. Fundamental information about the structure and interactions of photons could appear as systematic departures from Planck's Law, though finding these would probably require measurements at higher temperatures than will be considered here. But the essentials of our technique, which is the use of interferometric spectroscopy and self-consistent calculations, could still be applied. Suitable high temperature sources might be found among the various gas discharge devices that have been investigated in thermonuclear fusion research programmes.

As far as we are aware, no measurements of black body radiation over a wide frequency range have been reported since those of Coblentz more than fifty years ago^{2,3}.

The Spectrum and the Interferogram of a Black Body Source

Planck's Law gives the spectral distribution of power emitted by a black body source at a given temperature T as

$$\frac{dP_\theta}{d\theta} = \sigma A T^4 \left| \frac{15}{\pi^4} \frac{\theta^3}{e^\theta - 1} \right| \quad (1)$$

where θ is the temperature-reduced frequency defined by

$$\theta = \frac{hc}{kT} \bar{\nu} \quad (2)$$

and $\bar{\nu}$ is frequency in cm^{-1} . $dP_\theta/d\theta$ is expressed as watts per unit θ and is shown in Fig. 2a. The constant A includes the size of the source and the cone angle of the radiation. σ is Stefan's constant which, in terms of Planck's constant h and

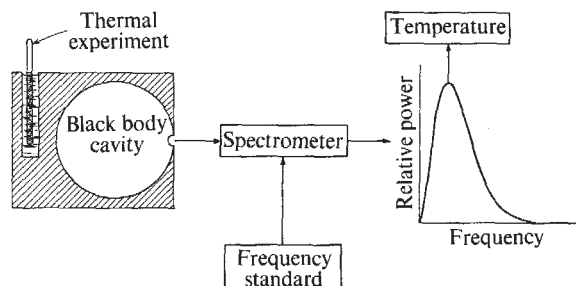


Fig. 1 Schematic arrangement illustrating measurement of temperature in terms of frequency.

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Boltzmann's constant k , is given by

$$\sigma = \frac{2\pi^5}{15} c^{-2} h^{-3} k^4 \quad (3)$$

Corresponding relationships between radiated power and path difference are of interest, not only because path difference is the independent variable actually used in interferometric measurements, but because formulations in terms of both frequency and path difference are useful in calculating the information content of observations.

When power is measured as a function of path difference X it is convenient to define a quantity φ which is the temperature expanded path difference

$$\varphi = \frac{kT}{hc} X \quad (4)$$

Power as a function of φ is related to the spectrum by a Fourier transform

$$P_\varphi = \frac{1}{2} \int_0^\infty \frac{dP_\theta}{d\theta} \cos(2\pi\theta\varphi) d\theta + \frac{1}{2} P_0 \quad (5)$$

where P_0 , the total power radiated, is obtained by integrating equation (1). For a black body

$$P_\varphi = \frac{1}{2} \sigma A T_s^4 \left[1 + 15 \left\{ \cosh^2(2\pi^2\varphi) [3\cosh^2(2\pi^2\varphi) + 2] - \frac{3}{(2\pi^2\varphi)^4} \right\} \right] \quad (6)$$

P_φ is expressed in watts and its form is shown in Fig. 2b. Equation (6) was first derived by Bourret⁴ and has been discussed by Kano and Wolf⁵.

The observed quantity in a black body spectral measurement is the power reaching a detector in a specified frequency interval. This will depend on temperature and the geometrical factor A , but also on $\epsilon_{\nu(T)}$ and D_ν , which we call spectral efficiency factors

$$\frac{dP_\theta}{d\theta} = \frac{15}{\pi^4} \sigma A T^4 \epsilon_{\nu(T)} D_\nu \frac{\theta^3}{e^\theta - 1} \quad (7)$$

$\epsilon_{\nu(T)}$ is the ratio of the power emitted by the source to that from a true black body at the same temperature. It will in general be a function of frequency and of source temperature but, for a well designed source, it will be close to unity and slowly varying with both frequency and temperature. D_ν will be a function of frequency but is independent of source temperature. It is the product of two factors, the spectral transmission of the whole path from source to detector and the spectral absorptivity of the latter. It will measure, as a fraction, the ratio of the signal from the real detector to that from an ideally black detector when the path from the source to detector is free from absorption.

An expression for P_φ corresponding to equation (7) would include quantities corresponding to the spectral efficiency factors as convolutions.

Black Body Temperature Measurement

To achieve the objective of measuring temperature in terms of frequency we would need: (1) A radiator which is as good an approximation to a black body as can be made using previous experience^{2,6,7}. (2) A Michelson interferometer with high information throughput⁸ for the appropriate frequency region with a laser frequency standard. (3) A detector and measuring system giving relative power values with adequate sensitivity, linearity, and dynamic range. (4) A measurement

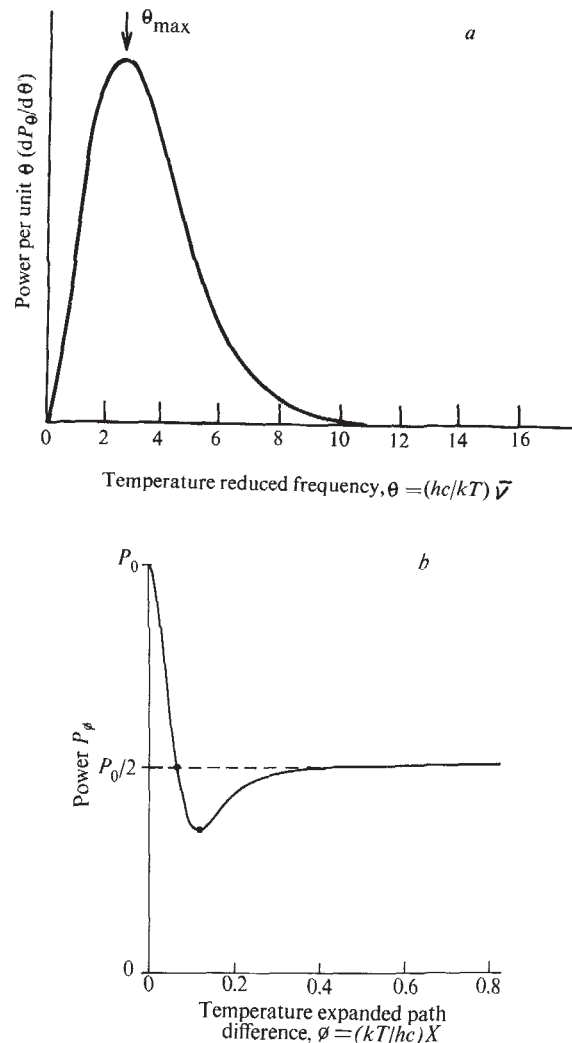


Fig. 2 Form of black body spectrum (a) and interferogram (b) as function of appropriate variables.

technique which provides sufficient information and redundancy to give a complete solution to the chosen problem. (5) A computer program which will translate the observables into the required parameters.

To demonstrate feasibility, we calculate the available amounts of information with realistic detector and system limitations for several values of temperature and accuracy using the optical arrangement of Fig. 3. The source temperature would be fixed and the maximum number of meaningful measurements made as a function of path difference by moving the interferometer mirror. The temperature would then be changed and the operation repeated. No other observations beyond this scheme of measurement are required.

The numerical parameters of some proposed measurements, using the symbols defined in Table 2, are assembled in Table 2. In the first example we aim to measure a temperature of 1,000 K to an accuracy of 0.1 K. For a first estimate we take $\epsilon_{\nu(T)} = D_\nu = 1$.

We note in the example that $n_2 \gg n_1$ so that there is adequate basic sensitivity, but to specify temperature in terms of frequency and use only relative power measurements, we should use the largest permissible spectral range. The information content of a spectrum depends on the number of meaningful subdivisions of the frequency scale and the number of meaningful subdivisions of the power ordinates. To stress the frequency scale we should use maximum spectral resolution but there is an interdependence of these quantities because the resolution is itself determined by the maximum permissible path difference which in turn is determined by detector noise. The spectral

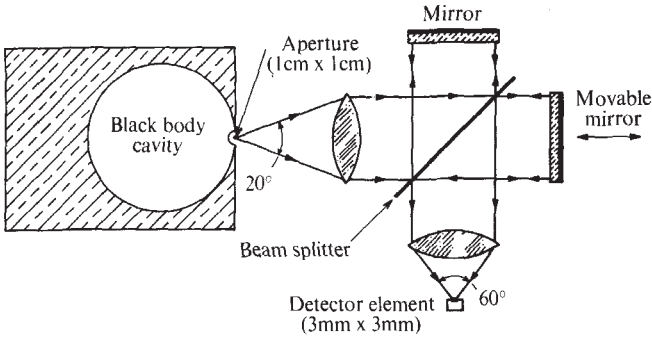


Fig. 3 Schematic of black body source and interferometer proposed for temperature-frequency measurement. The dimensions shown are those used in calculation of the parameters of Table 2.

resolution $\delta\nu$ comes from finding the value of path difference X_c at which the ordinate P_ϕ differs from the asymptotic values $1/2P_0$ by an amount equal to δP from which $\delta\nu$ is given by $1/X_c$.

The values of $P_0 = 3 \times 10^{-2}$ W and $\delta P = 10^{-9}$ W suggest that a large range in values of power ordinates will have to be measured and against this we must respect limitations of

Table 2 Numerical Values for Parameters in Interferometric Measurements on Black Body Sources to Establish Frequency Based Temperature Values

Example	I	II	III	IV
T	1,000	1,400	270	90
ΔT	0.1	0.01	0.01	0.01
n_1	10^4	1.4×10^5	2.7×10^4	9×10^3
P_0	2.9×10^{-2}	1.1×10^{-1}	1.5×10^{-4}	1.9×10^{-6}
δP	10^{-9}	10^{-11}	5.77×10^{-12}	3.16×10^{-12}
n_2	2.9×10^7	1.1×10^{10}	2.6×10^7	6×10^5
L	1,000	5,000	5,000	5,000
τ	1	1	3	10
$\bar{\nu}_{\max}$	1,960	2,740	529	176
$\bar{\nu}_c$	4,000	5,600	1,080	360
X_c	1.16×10^{-2}	3.67×10^{-2}	4.2×10^{-2}	4.9×10^{-2}
δX	1.25×10^{-4}	8.9×10^{-5}	4.63×10^{-4}	1.39×10^{-3}
$\delta \bar{\nu}$	86	27	24	21
N_t	94	370	92	36
N_s	47	185	46	18
$\mathcal{N}$	2.3×10^4	3.0×10^5	7.4×10^4	3.1×10^4
t	94	370	276	360

Table 1 Definition of Symbols used in Table 2

T	Black body temperature to be measured in degrees Kelvin.
ΔT	The accuracy being sought in the value of T .
$n_1 = \frac{T}{\Delta T}$	Is a measure of the amount of information needed to solve the problem.
P_0	The total power measured in watts available at the detector with the optical system shown in Fig. 3.
δP	The minimum measurable power set by detector noise with an integration time τ .
$n_2 = \frac{P_0}{\delta P}$	A measure of the maximum amount of information available from a single observation in time τ .
τ	Integration time for single observation at a particular value of path difference.
L	A measure of the dynamic range of the measuring system. $L, \delta P$ is the maximum power that the system will be required to measure.
$\bar{\nu}_{\max}$	The frequency in cm^{-1} at which the black body spectrum has its maximum power density.
$\bar{\nu}_c$	The highest measured frequency in cm^{-1} from the source. Cutoff filters will be used to choose this value.
X_c	The value of path difference measured in centimetres at which the interferogram power ordinate differs by δP from the asymptotic value of power $P_0/2$ measured at very large path difference.
$\delta X = 1/(2\nu_c)$	The increment in path difference measured in centimetres at which the interferogram will be sampled.
$\delta \bar{\nu} = 1/X_c$	The spectral resolution, or smallest meaningful subdivision in frequency measured in cm^{-1} .
$N_t = \frac{X_c}{\delta X}$	The number of interferogram samples.
$N_s = \frac{\bar{\nu}_c}{\delta \bar{\nu}}$	The number of spectral points
$\mathcal{N} = \sum_{x=0}^{X_c} \frac{P_\phi}{\delta P}$	The number of information elements in the interferogram. The value of P_ϕ has been computed from equation (6), but was restricted to a maximum value $L, \delta P$.
$t = N_t \tau$	Total time for measurement.

Other symbols are defined in the text.

detector systems in linearity and dynamic range. Corrections for departures from linearity can be included in the analysis, but it is important not to exceed some reasonable value for dynamic range. We assume that the maximum acceptable power for measurement is 10^3 times the smallest signal, and that any signals greater than this will be attenuated by known factors to bring them within this limit. Technically this is a primitive and wasteful solution but it allows us to calculate lower limits to the amount of available information. All the relevant quantities have been given in Table 2 and from them the number $\mathcal{N}$ of information elements per interferogram has been calculated. By multiplying N_t by the detector-integration time τ the total time t to measure one interferogram has been derived.

In examples II, III and IV the parameters for temperatures of 1,400 K, 270 K and 90 K are given. In these examples where an accuracy of 0.01 K is sought, we propose that a helium cooled detector with a lower noise level should be used and that a means be found to extend the dynamic range of the measuring system. The results show that acceptably short observation time can still be realized.

Observational Redundancy and the Data Reduction Problem

The factors $\epsilon_{\nu(T)}$ and D_ν will be determined within the main scheme of observations by exploiting different spectral distributions associated with different source temperatures and values of temperature will come from fitting observations to Planck functions over the whole usable spectral range. In this full redundancy of the measurements will be exploited.

In example I, the total of $\mathcal{N} = 2.3 \times 10^4$ information elements spread over fifty spectral entries would be more than sufficient to give the required temperature accuracy measured by n_1 , if it were not for the need of additional information to determine values of $\epsilon_{\nu(T)}$ and D_ν . These could in principle each require an additional 10^4 elements as an upper limit but by good design the actual number can be made smaller. But even if the maximum of 3×10^4 information elements were needed to specify the first value on the temperature scale, successive values close enough in temperature that the emissivity is unchanged will require only 10^4 elements each. Each interferogram will add 2.3×10^4 information elements so that, as the number of temperature entries is increased, the amount of information available will rapidly overtake the needs of the problem. When interferograms over a range of temperature have been recorded, an internally consistent set of results will

be produced which can, in principle, be analysed explicitly for temperature values and for values of $\epsilon_{\nu(T)}$ and D_{ν} .

Conventional methods of data reduction using least squares methods applied to this kind of problem often lead to numerically ill-conditioned sets of equations. To avoid these difficulties we propose that mean square estimation theory as discussed by Franklin⁹ should be used. This method uses a computer algorithm which guarantees that ill-conditioning will not occur and which is designed to include information about noise and errors. Such a scheme can also help in choosing the data format to give the greatest accuracy in temperature.

A favourable experimental factor in our measurement scheme is the comparatively small time needed to measure one temperature. Table 2 shows that measurement at quite small temperature increments is practical.

Black Body Spectra and Temperature Frequency Values

The first motivation of our proposal is, in the long term, to dispense with material standards and so with arbitrary temperature units. Temperature would then be measured in frequency units and the need for Boltzmann's constant would disappear. Because a temperature value uniquely specifies a Planck function and this has a range of frequency values, there is a need to specify a single frequency to represent temperature. One choice might be the value corresponding to $\bar{\nu}_{\max}$ which is

$$\bar{\nu}_{\max} = 2.82(k/hc)T$$

but arbitrarily we prefer the simpler relation

$$\bar{\nu}_0 = (k/hc)T$$

making the single value of frequency which measures temperature $\bar{\nu}_0 = 0.35 \bar{\nu}_{\max}$.

History of Fundamental Constants derived from Black Body Spectra

Many spectroscopists might regard the measurement of black body radiation as an unpromising field, yet no branch of spectroscopy can claim a more important discovery than Planck's quantum introduced in 1900 to explain the results of Lummer and Pringsheim¹⁰. Planck's contribution, however, went further¹¹. The ratio c_1/c_2 of the constants in his formula gave a value for Boltzmann's constant, k , which with the gas constant R gave Avogadro's number, N , in good agreement with present day values. Avogadro's number with the Faraday gave a value for the electron charge which differed from modern results by about 2.5% and was by far the most accurate contemporary determination. At one stroke Planck had brought new numerical order to microscopic physics and surprisingly had done this by using observations of continuous spectra. This feat is even more remarkable when we consider the limitations of the spectroscopic techniques available to Lummer and Pringsheim. Planck's secondary achievement has not been given the attention it deserves, nor in our view has the power of black body spectroscopy to reveal new things been fully recognized.

Photon Properties from Black Body Spectra

The use of black body radiation in specifying temperature assumes that Planck's Law completely describes the statistical behaviour of photons as bosons. New measurements with perhaps one hundred times the accuracy of their predecessors might show departures from Planck's Law which could be interpreted in terms of photon structure. Such a possibility has been considered by Perkins¹² in connexion with a neutrino theory of a composite photon. Photon-photon interactions have also been invoked in a recent attempt to explain astron-

omical redshifts¹³ indicative of current interest in photon properties. Because there does not yet appear to be any prediction of the magnitude of departures from Planck's Law, there is little doubt that finding such a phenomenon would be of very great value.

History shows that black body spectroscopy is a powerful tool: we believe that the time has come to try it again to see what new qualitative information about radiation it can be made to yield.

Overall Method

We are proposing to measure black body radiation by interferometric methods which are well suited to measuring continuous spectra over wide frequency ranges. Values of temperature and empirical parameters describing the departure from ideality of source and detector would be constrained to fit the observations and Planck's Law by making maximum use of redundancy. The numerical fits would be made by iterative self-consistent reduction schemes which are in use in other branches of physics.

Estimates show that standard temperature values covering the range from 90 K to 1,400 K with an accuracy of 0.01 K could be established without the need for excessively long observation times. These values do not necessarily represent the limits of temperature or of accuracy that might ultimately be achieved. In the range considered, six material fixed points are defined in the present practical scale but the spectroscopic system would require no definitions except a frequency standard. This would bring temperature within the framework of the mass-length-time measurement system which must surely be an aim of any progressive programme to improve thermometry.

The technique we propose could extract perhaps a hundred times the amount of information available from previous black body spectra and would have the prospect of showing systematic departures from Planck's Law. Such phenomena would be of great interest for the new fundamental information they could give on photon statistics. It seems likely that higher temperatures than we have considered for thermometry will favour the discovery of anomalous photon behaviour but the essentials of the measurement technique would be the same when applied to suitable source.

We do not underestimate the numerous technical problems which will have to be overcome to implement our proposal, but our analysis shows that worthwhile end-points could be achieved. Given the benefit of up-to-date techniques, black body spectroscopy could still have much to contribute to physics.

This investigation had its beginnings for H. A. G. at the National Physical Laboratory, Teddington, England, and was continued while he was a senior research fellow at the National Bureau of Standards. We thank Dr E. U. Condon for drawing our attention to Planck's derivation of a value for the electron charge and several colleagues for their comments.

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Evolution of Ribonuclease in Relation to Polypeptide Folding Mechanisms

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Sequences from seven pancreatic RNAases show a highly variable structure. The evolution of apparently functionless parts of a protein is thought to be based upon requirements for the polypeptide folding process.

In each of the series of homologous proteins for which sufficient data¹⁻³ exist for comparisons, some positions in the polypeptide chain are occupied by a single type of invariable amino-acid. For example, cytochrome c has 29 positions that are invariant in 34 species from fungi to man^{2,3}. The most obvious interpretation of invariance at a given codon is that the residue specified is essential for the function of that protein, either directly or because it is contributing irreplaceably to maintenance of the active structure. This has been proposed¹⁻³ for the invariant residues in cytochrome c, and is clearly indicated in the haemoglobin chains by the critical situation, for example haem-bonding, in the structure⁴ of at least 5 of their invariant residues. On the other hand, the cause of the various degrees of change at the variable positions remains uncertain^{1-3,5-9}. Powerful arguments have been raised^{5,6}—and contested⁷⁻⁹—to interpret them largely in terms of neutral mutations, giving “non-Darwinian evolution” at the protein level.

To examine the range of variability, enzymes should be chosen that are not under very strong selection pressure, ones that are less essential to life than cytochrome c and haemoglobin. Since pancreatic RNAase has this¹⁰ and other¹¹ advantages, we are engaged in the sequence determination of pancreatic RNAases from diverse species. The bovine enzyme is available as a reference with respect to amino-acid sequence¹², crystallographic structure^{13,14} and structure-activity relations^{11,14}. We present here comparisons of the N-terminal region of this polypeptide in seven species, relating these to principles governing the mutability of protein primary structure.

Sequence Determination

The sequences of the pancreatic RNAases from the pig¹⁵ and the rat¹⁶ are known. RNAase from the pancreas of the Virginia deer, American bison, red kangaroo and snapping

turtle was purified to electrophoretic homogeneity by methods to be described elsewhere. Either the native or the performate-oxidized¹² protein was used, without difference in the results except for the cysteic acid (position 26) in the latter. Each protein (8–12 mg) was degraded stepwise on the Beckman Protein Sequencer¹⁷ with identification of each successive phenylthiohydantoin by gas chromatography (both with and without silylation). The identity of each residue was confirmed by thin-layer chromatography of the phenylthiohydantoin¹⁸, and again, where helpful, by hydrolysis of the latter (6 M HCl, 24 h, 140° C, *in vacuo*) and amino-acid analysis (Beckman Analyzer) of the surviving liberated amino-acid. Each protein was sequenced thus at least twice, and the yield per repetitive cycle was high enough for the series to extend beyond position 30 with clear-cut recognition of the residue at each position listed. An independent manual confirmation of most of the turtle enzyme sequence reported here will be described in a subsequent paper on the full sequence of that protein.

Evolutionary Rates

Judging from four known vertebrate pancreatic RNAases (Table 1), substitutions in this sequence have occurred in its evolution more rapidly than in any other protein so far investigated. The only faster rate known is that of an isolated (“hypervariable”) segment within a larger, more constant protein, as in the fibrinogen and the pro-insulin molecules (Table 1).

In fibrinogen and pro-insulin, the variable segments are discarded in forming the functional protein, and therefore can escape selection pressure acting on the protein. So far as is known they are virtually functionless once released. Their rate of acceptance of replacements has been presumed, therefore, to approach the maximum possible rate of molecular evolution of a protein, which, it has been postulated, is the rate of fixation of neutral mutations by genetic drift^{3,5,6}. It has been estimated that this rate in the most variable positions of the fibrinopeptides is consistent with that expected on the basis solely of transcription errors in DNA replication^{19,20}. Pancreatic RNAase as a whole has accepted mutations at about one-half of the rate of the fibrinopeptides. As the enzyme has highly functional parts, some other parts must have evolved as rapidly as the fibrinopeptides.

Conserved Residues

About the first one-quarter of the sequence is now available in seven vertebrate species (Table 2). In this set there are, so

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far, eleven invariant residues, as well as two, positions 3 and 13 (numbering throughout as in the bovine), that show only very conservative substitutions.

The loss of the N-terminal Lys in two species recalls its known non-injurious removability from bovine RNAase²¹. Similarly, for Glu-2, amidated in the pig, there is evidence from synthetic studies^{22,23} that it is not truly essential; nor is²² Thr-3. The N-terminal region of bovine RNAase is held in position largely by side-chain interactions^{13,14} of Phe-8, His-12, Asp-14 and Tyr-25, and these are invariant. Met-13 also makes a strong hydrophobic contact; chemical studies show it to be important but not unique, being replaceable by norleucine^{23,24}. The replacement by Val (turtle), therefore, is not entirely surprising, but the size difference from Met, and the large changes also tolerated at positions 4, 5, 6 and 9, suggest that the secondary structure in this tail, largely helical in the bovine^{13,14}, differs in turtle RNAase. Ala-4 makes a hydrophobic contact of the tail, but this appears dispensable. (Structural interpretations in this paper are made on bovine RNAase A on the basis of a Kendrew skeletal model built by Shirley Drescher and E. A. Barnard from the data at 2 Å resolution of G. Kartha.)

Table 1 Amino-acid Replacements in Evolution of Homologous Proteins

Protein	% Changes from cow	Substitutions per amino-acid site †	Rate per year
Pig	Reptile	Series compared *	(× 10 ⁹)
RNAase	22	54 (Cow, pig, rat, turtle)	2.1
Insulin	1	(Mammals, birds)	0.20
Cytochrome c	0	9 (Eukaryotes)	0.25
Haemoglobin	12	(α, vertebrates)	0.75
Lysozyme		(Human ⁴² , 4 birds ⁴³⁻⁴⁵)	1.4
Other protein series		(2 species only)¶	0.01-0.8
Segments			
Pro-insulin C-peptide	38	(Human, cow, pig)	2.6
Lysozyme		(Human, 4 birds) ‡	3.5
Fibrinopeptides	41	57§ (A and B, vertebrates)	4.5
Fibrinopeptides	56	(A4-7, and B9-20)	8.3
RNAase	60	74 (15-24)	8.5

* For proteins other than RNAases, and evolutionary time estimation, see refs. 1, 3, 5. The RNAase value for the snapping turtle is derived from our unpublished data on about 90% of the sequence.

† The mean rate of observed substitution per amino-acid site has been corrected for the statistical factor⁹ due to mutations occurring at a site already mutated.

‡ The external loops that occur in both the human leukaemia and hen egg white lysozyme structures⁴⁶ at (hen) positions 72-79, 85-91 and 97-106 are compared in these and the duck⁴³, turkey⁴⁴ and quail⁴⁵ sequences.

§ Lizard; fibrinopeptide A only.

|| Changes at these hypermutable (ref. 20 and Table 2) chain positions for mammals where the sequence there is known.

¶ Estimates made where only two species (in eukaryotes) are available for comparison of each protein: histones, carbonic anhydrase, trypsinogen, glyceraldehyde phosphate dehydrogenase^{1,3}; glutamate dehydrogenase⁴⁷. The special genetic case of the immunoglobulins, and microorganisms, are excluded from these considerations.

His-12 (conserved) is an active centre group^{11,14} in the cow, and also¹¹ the kangaroo and turtle, RNAases. The conservation of Lys-7, which is close to the active centre, is interesting since high (but not native) activity is found with Ala-7 (E. Scoffone, personal communication) or norleucine-7 substitution²³. The side-chain of Arg-10, also conserved, may bond^{22,23} to the carboxyl of Glu-2, or, alternatively, contributes a positive charge for RNA binding. Cys-26 (and all known half-cystines in these proteins)

Table 2 N-Terminal Sequences of Ribonucleases

	1	5	10	15	20	25	30
Cow	Lys	Glu	Thr	Ala	Ala	Ala	Met
Bison	Lys	Glu	Thr	Ala	Ala	Ala	Met
Deer	Lys	Glu	Thr*	Ala	Ala	Ala	Met
Rat	Gly	Glu	Ser	Ala	Ala	Ala	Met
Pig	Lys	Gln	Ser	Pro	Ala	Ala	Met
Kangaroo	Glu	Thr	Pro	Ala	Ala	Ala	Met
Turtle	Glu	Thr	Arg	Thr	Ala	Ala	Met

The deer is *Odocoileus virginianus*, the bison (buffalo) is *Bison bison*, the kangaroo *Macropus rufus*, and the turtle *Chelydra serpentina*. The kangaroo sequence beyond 21 was not examined (owing to lack of material). Cow, pig and rat sequences are from refs. 12, 15, 16. Invariant residues are in bold type.

* Ser also occurred here, in the enzyme purified from pooled pancreas. † Identity uncertain: at positions 21 and 22 this may be due to a carbohydrate attachment at an Asn-21.

are invariant. An Arg near the buried (bovine structure) 25–26 Tyr-Cys group appears to have been deleted before the origin of the mammals. The Met-Met dipeptide at 29–30 is invariant, and has been suggested to be involved in hinge-like changes during binding in the active centre¹¹. All the invariant or strongly conservative residues here would be subject to natural selection pressure in terms of enzymic activity. In these species, this activity is physiologically significant^{10,11}.

Hypervariable Segment

Sequence 15–24 varies at every position within the six or seven species where it can be compared (Table 2). Even closely related species such as the cow and the bison can differ at 50% of positions in this continuous stretch. The differences in this series are greater than those within the fibrinopeptide phyletic series, in which there is only 7.5% difference between the cow and the European bison. There is no conservation of net charge. In going from turtle to the mammalian RNAase sequences, six of these ten positions require two or more base changes.

Table 3 Amino-acid Selection in Hypervariable Segments

	Fibrino- peptide A	Ribo- nuclease 15–24	Pro- insulin C-peptide	Random protein (%)
Gly	24	1	22	7.2
Glu	13	4	13	4.7
Asp	13	3	1	3.6
Ala	9	11	11	6.0
Ser	8	21	2	8.6
Thr	6	7	0	6.9
Val	6	0	3	6.1
Phe	6	0	0	2.2
Leu	3	0	14	7.9
Lys	3	2	0	5.5
Pro	3	7	9	5.0
Ile	2	0	0	5.2
Gln	1	1	6	3.9
His	1	0	0	3.0
Asn	0	5	1	4.2
Arg	0	1	0	10.7
Tyr	0	1	0	3.1
Trp, Cys, Met	0	0	0	6.0
	98	64	82	

The total occurrence of each amino-acid in these sequences is listed. Six species were used for both the fibrinopeptide and the RNAase cases—cow, deer, bison, pig, rat, and turtle or lizard (and kangaroo was included in RNAase only); for pro-insulin⁴⁰, human, cow and pig only. The last column shows the percentage composition of a protein dictated randomly by the genetic code, using a genome corresponding to the mean of known vertebrate proteins, as calculated by King and Jukes⁵.

This hypervariability can be correlated with a lack of any contribution of this segment to either the enzymic activity or the maintenance of structures required for that activity: (i) In the RNAase A structure, residues 15–24 are remote from the active centre, and in an external loop which makes only slight interaction with the rest of the structure. This is the only part of the native structure where proteases^{25,26} can gain access to attack. (ii) A bulky polysaccharide chain is attached at position 21 in porcine RNAase¹⁵, which is highly active. (iii) When cleaved with subtilisin²⁵ at bond 20–21 to give bovine RNAase S, the positions of residues 15–24 in the crystal structure are considerably changed¹⁴. The chain at 16–23 is then poorly defined¹⁴, suggesting mobility. Yet RNAase S is fully active.

(iv) Excision of residues 15–20 from bovine RNAase by a synthetic method²³, or by proteolysis²⁷, removes no enzymic activity. (v) Excision of residues 21–25, by another synthetic route, gives *per se* no reduction in activity²⁸.

If this segment is totally dispensable, does its mutability represent, therefore, the limiting rate of neutral mutation^{5,6} in protein evolution? Its replacement rate is faster than that of the pro-insulin C-peptide, or of the fibrinopeptides taken as a whole, but equal to that of the most variable segments²⁰ within the latter (Table 1). Yet the replacements actually occurring are very different between these series, and are far from random (Table 3). The variability in each series appears able to draw upon only a restricted group of amino-acids. Thus, while glycine would be expected to occur frequently if chosen randomly on the basis of genetic coding or its usual abundance in proteins⁵, it occurs thus in the fibrinopeptides but not in the RNAase segment (Table 3). If the changes represent random neutral mutations, the probability that several of these within a single gene occurred together in adjacent codons in the separation of closely-related species, and were all fixed in the population by drift to give a unique local sequence, must be vanishingly low. Polymorphism¹ would then be expected to be very high here, but was detected clearly at one position in the deer protein only. While very minor variants could certainly be undetected in typical sequencing operations, the great majority of the molecules present from each species must have had the same sequence in the fibrinopeptides, and in the RNAases from the turtle, where tissue from several hundred animals was pooled, or the kangaroo, several tens, or the rat. Similarly, in a test of 250 human fibrinopeptide genes, no polymorphism was detectable electrophoretically²⁹.

Natural Selection of Sequences

The available limited evidence on hypervariable regions indicates that there is still an evolutionary constraint on them, albeit much less stringent than the constraints on function-maintaining regions. We propose that there is a selection pressure acting on all regions of a protein sequence in evolution, that is, truly neutral mutations do not, in fact, generally become fixed in speciation. It is useful here to distinguish between: (1) Selection acting on function, on parts of the protein molecule that contribute, directly or by structure-maintenance, to its observable biological activity. Thus, for cytochrome c, this would include mutations affecting in any way its electron transfer function, including the parts of its surface which interact with the other components involved, cytochrome oxidase and reductase³. (2) Selection acting on availability, to maintain other features of the intact protein which ensure that it is sufficiently available for function. This would include any structures in cytochrome c which ensure that it is transported to and bound in the mitochondrial membrane, prevent undesirable complexes with other components, or affect its catabolism, isoimmune reactivity, and other properties. (3) Selection acting on polypeptide folding. We postulate that all regions in a polypeptide chain are subject to natural selection to some degree for their influence on the process of folding up to the correct final tertiary structure. Such selection will usually be negative, deleting incompatibility. This effect can be exerted only for an extremely short period in the lifetime of the molecule, on the kinetics of correct folding and disulphide formation in the nascent polypeptide chain. A mutation of type 1, affecting function in the final state, need not interfere in this manner, and *vice versa*. Examples are known in RNAase A of a chemical modification at a single amino-acid which does not remove activity but, after unfolding, prevents correct refolding³⁰.

It is usually agreed that nucleation centres occurring in the folding structure of a polypeptide must direct the process, and it has been proposed that these are interacting helical or other ordered sub-assemblies^{31,32}. Scheraga *et al.* have noted

tetrapeptide β -bends in the backbone of RNAase and other proteins, which they deduced to be major directing influences for this dynamic process³¹. The location of β -bends in the final structure, however, may not be a sufficient record of transient directive interactions that occurred during the folding process. Thus one β -bend cited³¹, at residues 16–19 in RNAase S, occurs in that structure but not in the same tetrapeptide in the native protein, RNAase A. In addition, hydrophobic side-chains will usually be preferred for the positions in the interior of a protein, and *vice versa*⁴, giving rise to a well-known major driving force for the folding process³³. Beside the conservative effect³⁴ acting on residues required for the maintenance of the active conformation, this factor can still give a selection effect of type 3. While a single change to a non-polar residue in an external functionless region might be accepted in folding, further adjacent ones would tend to be disfavoured.

In the hypervariable segment, the unexpected absence of glycine can now be explained, as a glycine residue encourages other types of neighbouring residue to form a β -bend³¹; mutations to glycine here would have a higher probability of an unwanted directive effect. Similarly, the most hydrophobic amino-acids are avoided. They occur frequently in the fibrinopeptides and the pro-insulin C-peptide (Table 3) but some other type of structure must occur in their parent molecules. We suggest, then, that obstructions to the correct folding, that would arise from the formation of inappropriate helices or β -bends for example, lead to a sifting of the mutations that occur in otherwise neutral positions. The type of selection occurring is therefore dependent upon the rest of the structure, differing in each case but not random. In lysozymes, also, limited evidence (see Table 1) indicates that surface loops (containing³¹ four β -bends) have a rather similar hyper-variability to that in the RNAase loop.

In cytochrome c and RNAase³⁵, replacements tend to occur in linked groups, "co-various"². We attribute these co-various to selective forces 2 and especially 3, rather than 1; thus, when one residue mutates, the correct folding is often likely to be easiest again if certain others mutate also.

Mutations that tend to obstruct the folding process can lead to various intensities of selection pressure. The folding to the correct structure might be totally prevented, in which case no active protein will be isolated. Or the folding to the stable structure might eventually be possible, but suffer delay. The latter case may be physiologically deleterious but may not be recognized in simple experimental tests of refolding. Decisive tests would require synthesis of a "wrong" sequence at this site without a break in the chain, and careful kinetic comparisons of refoldings. It is interesting that bovine RNAase S-protein²⁵ does not refold correctly, although it does with S-peptide present³⁶. On our view, undesirable directing of folding can arise at a particular position in the chain from the presence of only certain amino-acids there; this would explain the observation that certain derivatives of RNAase A in which the backbone is cleaved³⁶, or having esterified carboxyls or acylated lysines^{37,38}, can still refold correctly (even if more slowly). Long polar chains added³⁸ may, in fact, ensure that the residue modified remains external during the folding process. Bulky non-polar substituents at the same positions do interfere with refolding³⁹. In the pro-insulin molecule, even a single cleavage at the C-peptide region can prevent correct refolding⁴⁰. The same is known to be true for a cleavage at the fourth bond from the C-terminal of RNAase⁴¹.

If, then, as we argue, truly neutral mutations very rarely become fixed in evolution, the rate of replacement in the fastest-evolving protein regions known (Table 1) does not represent a universal neutral mutation rate. The latter would be faster than the edited process which is seen phylogenetically. Since the principles of protein architecture and folding appear to be universal, the observed substitution rate, restricted by them, will reach about the same maximum value in diverse protein lines of evolution. This provides, therefore, a totally different

explanation for the facts of an apparently high overall rate of substitution and its near-constancy, which have been taken^{5,6,20} as prime evidence for a neutral mutation mechanism.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Radio Source Counts and Redshifts in Steady State Cosmology

THERE appears to be continuing confusion as to whether or not counts of extragalactic radio sources are compatible with the steady state theory. Ryle and Clarke¹ found considerable discrepancies between the observed counts and those predicted on the basis of steady state. Hoyle² argues that the source counts are in agreement with the steady state theory except for a deficiency of only 5 sources per steradian at the bright end. I present here an explicit derivation of source counts expected in the steady state on the basis of identifications and redshifts of a complete sample of radio galaxies and quasi-stellar sources.

Identifications and redshifts exist now for all 3CR sources that are more than 15 degrees from the galactic equator and that have a 178 MHz flux density S_{178} exceeding 30 flux units (1 f.u. = 10^{-26} W m⁻² Hz⁻¹). Table 1 gives the flux density S_{178} , the radio spectral index $\alpha = d \log S_\nu / d \log \nu$ and the redshift z for all 26 sources³⁻¹⁰. I have adopted the identification of the source 3C 61.1 as a galaxy in a cluster of galaxies¹¹ rather than a quasi-stellar object¹².

To derive source counts expected on the basis of flux densities and redshifts of a complete sample of sources, we use a method described recently¹³. Source counts corresponding to each of the sources in the sample are derived separately. For each source we compute the volume $V(> S_\nu)$ out to the redshift z' at which it would have an observed flux density S_ν at frequency ν . The relevant equations for the steady state cosmology are

$$2 \log z' + (1 - \alpha) \log (1 + z') = 2 \log z + (1 - \alpha) \log (1 + z) + \log S_{178} - \log S + \alpha \log (\nu/178) \quad (1)$$

$$V(z') \sim \ln (1 + z') - \frac{z' (2 + 3z')}{2(1 + z')^2} \quad (2)$$

where the equation¹⁴ for $V(z')$ includes the effect of continuous creation. Similarly we compute the volume V_m out to the redshift z_m at which the source would have a flux density of 30 flux units at 178 MHz. Each source contributes to the radio source count $N(> S_\nu)$ proportional to $V(> S_\nu)$, normalized to unity over the volume V_m . The total predicted source counts are

$$N(> S_\nu) = \Omega_s^{-1} \sum V(> S_\nu) / V_m \quad (3)$$

where Ω_s is the solid angle covered by the complete sample (5.1 steradians for the 3CR at $|b| > 15^\circ$). The above method has the advantage that the properties of the individual sources in the sample, such as the spectral index or even curved radio spectra, are transmitted into the derived source counts.

There is no reasonable doubt about the cosmological origin of the redshifts of the radio galaxies listed in Table 1. The source counts at 408 MHz corresponding to these radio galaxies as derived from equations (1) to (3) are given in Table 2.

The situation is different for the quasi-stellar sources. A complete sample of 33 quasi-stellar 3CR sources exhibits $\langle V/V_m \rangle = 0.75 \pm 0.05$ in the steady state cosmology if their redshifts are of cosmological origin¹⁰. This value of $\langle V/V_m \rangle$ is very significantly different from the value 0.50 expected for a

uniform distribution of objects in space as required by steady state. If the redshifts of quasars are non-cosmological and their distances relatively small, then the sample of 33 3CR quasi-stellar sources yields¹⁵ $\langle V/V_m \rangle = 0.57 \pm 0.05$. This value does not differ significantly from 0.50. Thus the steady state can accommodate the quasi-stellar sources only if their redshifts are mostly non-cosmological.

The distances of the quasi-stellar sources in Table 1 cannot be arbitrarily small, or the background temperature corresponding to their integrated effect to very large distances would become too large. A rough calculation shows that if the quasi-stellar sources in Table 1 have a cosmological redshift of 0.001 then the corresponding background temperature at 178 MHz is around 10 K, a substantial fraction of the observed 30 K (ref. 16). Hence a cosmological redshift of 0.001 represents the smallest distance scale for our quasi-stellar sources. Table 2 gives the source counts at 408 MHz corresponding to the quasi-stellar sources computed from equations (1) to (3) on the assumption that each of the five quasi-stellar sources in Table 1 has a cosmological redshift of 0.001.

We show in Fig. 1 the resulting expected total source counts, compared to the observed source counts taken from Pooley and Ryle¹⁷. The disagreement between the observed points and the predicted curve is very large.

Hoyle² has pointed out that the shape of the curve of the observed source counts and that expected for the radio galaxies are similar at the faint end and has argued that only 5 sources per steradian seem to be missing at the bright end. We have seen above that this is not the case if one considers radio galaxies and quasi-stellar sources together. We can, however, still adjust the distance scale of the quasi-stellar sources in an attempt to get some agreement in shape of predicted and observed counts at the faint end. The agreement should be

Table 1 Complete List of 3CR Sources with $S_{178} \geq 30$ f.u. and Galactic Latitude $|b| > 15^\circ$

3C	S_{178} (f.u.)	α	z
33	54.4	-0.67	0.0600
48 *	55.0	-0.56	0.367
61.1	31.2	-0.71	0.18
66	35.7	-0.70	0.0215
79	30.5	-0.77	0.2561
98	47.2	-0.74	0.0306
196 *	68.2	-0.76	0.871
219	41.2	-0.74	0.1745
227	30.4	-0.78	0.0855
234	31.4	-0.83	0.1846
270	51.8	-0.53	0.0041
273 *	62.8	-0.23	0.158
274	1,050.0	-0.79	0.0041
295	83.5	-0.60	0.4610
298 *	47.5	-0.98	1.439
310	56.0	-0.89	0.0543
317	49.0	-0.92	0.0351
327	35.3	-0.74	0.1041
338	46.9	-1.09	0.0303
348	351.0	-1.00	0.1540
353	236.0	-0.71	0.0307
380 *	59.4	-0.68	0.691
390.3	47.5	-0.70	0.0569
433	56.2	-0.72	0.1025
452	54.4	-0.76	0.0820
465	37.8	-0.72	0.0301

* Quasi-stellar source.

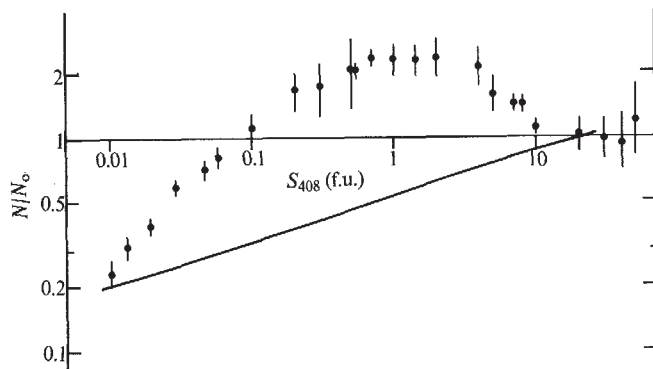


Fig. 1 Observed and predicted source counts $N(>S_{408})$ at 408 MHz. The observed counts represented by the dots are taken from Pooley and Ryle¹⁷. The ordinate is N/N_0 where $N_0 = 6.2 (S/15)^{-1.5}$ sources per steradian while S is in flux units ($10^{-26} \text{ W m}^{-2} \text{ Hz}^{-1}$). The curve gives the predicted source count for the steady state theory if the five quasi-stellar sources of Table 1 are assumed to have a cosmological redshift of 0.001.

judged on the basis of the differential counts rather than the integral counts, because a deficiency at the bright end would affect the integral counts at all flux densities. Fig. 2 shows the counts, n , per interval $\Delta \log S_{408} = 0.4$ (corresponding to one astronomical magnitude), divided by the counts expected for a uniform distribution in Euclidean space, normalized in accordance with the normalization of Fig. 1.

The effect of increasing the distance scale of the quasi-stellar sources is to lower the predicted counts progressively toward the faint end. For an assumed cosmological redshift of 0.02 for the five quasi-stellar sources of Table 1 the predicted source counts show a reasonable resemblance at the faint end to the observed counts as seen in Fig. 2. In this case the ratio between the observed counts and the predicted counts is at least a factor

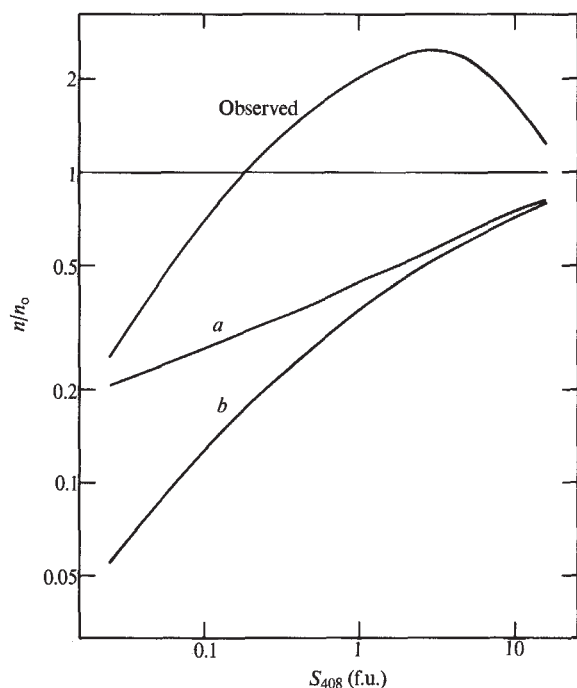


Fig. 2 Observed and predicted source counts $n(S_{408})$ per interval $\Delta \log S_{408} = 0.4$. The ordinate is n/n_0 where $n_0 = 9.3 (S/15)^{-1.5}$ sources per steradian per interval $\Delta \log S_{408} = 0.4$. The upper curve corresponds to a smooth representation of the observed points shown in Fig. 1. *a*, Predicted source count for the steady state theory if the five quasi-stellar sources of Table 1 are assumed to have a cosmological redshift of 0.001 curve. *b*, Similar treatment for a cosmological redshift of 0.02.

of 5 at the faint end. Hoyle's argument is that this is to be interpreted as a deficiency in the observed number of bright sources. This would mean that our complete sample of 3CR sources brighter than 30 flux units of Table 1 is deficient in numbers by a factor of 5; it should have consisted of 130 sources rather than 26. Because cosmological redshifts up to 0.46, or look-back times up to 38% Hubble time¹⁸, are represented in our sample, the deficiency could not be attributed to a particular place or time. We would normally expect that the population of a sample of N objects has a statistical error of $\sqrt{N}$. Thus we expect an uncertainty of around 20% in our sample of 26 sources. A model requiring as many as 130 sources simply does not fit the observations.

Table 2 Comparison of Observed Radio Source Counts $N(>S_{408})$ with Counts Predicted for the Steady State Theory

S_{408} f.u.	$N(>S_{408})$			
	Rg (ster ⁻¹)	$Rg + Qs$ Qs at $z = 0.001$ (ster ⁻¹)	$Rg + Qs$ Qs at $z = 0.02$ (ster ⁻¹)	Observed (ster ⁻¹)
25	2.31	2.91	2.92	2.9
10	7.45	9.85	9.75	13.5
4.0	23.2	32.7	31.5	86.3
1.6	69	107	98	422
0.63	198	346	293	1,496
0.25	538	1,114	822	4,630
0.10	1,431	3,653	2,205	12,450
0.04	3,626	12,052	5,525	29,500
0.016	8,878	40,012	13,052	64,100

Alternatively, we can derive the total number of bright sources that are "missing" by comparing 5 times the predicted integral counts given in the last but one column of Table 2 with the observed integral counts. We find that for S_{408} above 4 f.u. the number of missing sources is 71 per steradian. This is to be compared to the number of 5 per steradian given by Hoyle².

In conclusion, we find that whatever is the interpretation of the quasar redshifts, the observed radio source counts, identifications and redshifts are incompatible with the steady state cosmology.

I am grateful to Dr J. Miller of the Lick Observatory for allowing me to quote his observed redshift of 0.18 for the cluster of galaxies.

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MgI Emission in the Night Sky Spectrum

DURING September, October 1971 and April 1972 we observed a narrow region of the night sky spectrum in the vicinity of the 5183.62 Å MgI wavelength. Measurements were made with a scanning Fabry-Perot interferometer^{1,2} from the observatory at Izaña on Tenerife, Canary Islands, and consisted of spectral scans of up to 4 Å wide centred on the MgI wavelength. In all, some 350 spectra were obtained. Because the primary aim of the experiment was to study the zodiacal light, all spectra were recorded between evening and morning twilights, and most in the ecliptic plane. None was recorded during twilight.

The method of observation was to sample, for 48 s, each of up to 18 points across the spectral interval. Pulse counting electronics and a line printer recorded the signal level at each sample point. A second channel of pulse counting monitored the overall sky background over a wide waveband, thus allowing correction for fluctuations in sky transparency. The resolving power of the interferometer was 3,500, corresponding to an instrumental profile width of 1.5 Å.

Careful examination of the spectra revealed the presence of a small, variable, but undoubtedly real emission core at the centre of the zodiacal light Fraunhofer line. In general, because of the low signal levels, individual scans were not always sufficiently good to make measurements from, but scan averaging provided data of excellent quality. Fig. 1a shows a typical scan clearly showing emission, and 1b a scan in which there is no clear evidence for emission.

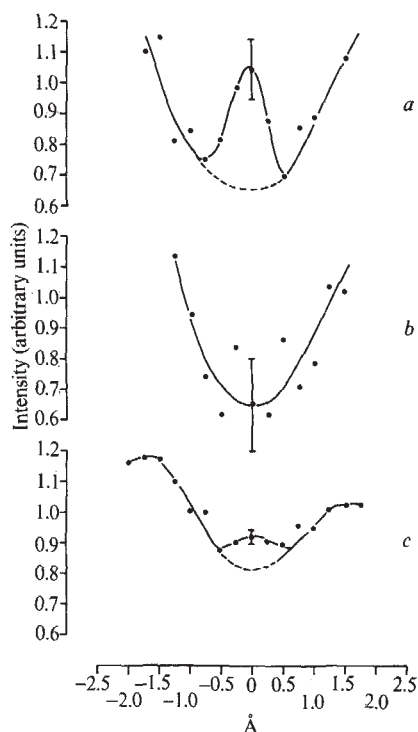


Fig. 1 Typical scans obtained in April 1972. *a* and *b*, Individual scans illustrating the quality of data (see text). *c*, Average of 7 scans recorded during the night of April 4/5. This clearly shows a significant emission.

The wavelength of the emission was determined by calibrating the interferometer with a magnesium hollow cathode lamp. The emission peak could be fixed to better than ± 0.2 Å from those individual scans which clearly showed emission. By combining the measurements from all such scans, the emission wavelength can be fixed at 5183.6 ± 0.1 Å. Reference to the MIT wavelength tables³ shows that lines of cobalt, europium, zirconium and magnesium occur very near to 5183.6 Å. We

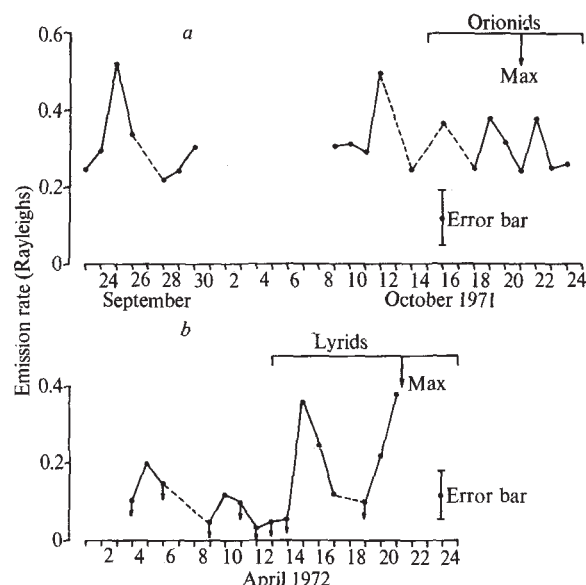


Fig. 2 Mean night-time emission rate as a function of time (see text). *a*, September, October 1971 data show little significant variation from night to night. The gap in data coincides with the period near full Moon. *b*, April 1972 data show emission rates lower than in *a*, with features coinciding in time with the Lyrid meteor shower. Vertical arrows on points denote upper limits.

identify the emission as being the 5183.618 Å line arising from the $3p^3P_2-4s^3S$ transition of MgI.

The well established enhancement of CaII emission at times of high meteor activity⁴ led us to look for a correlation between MgI emission and meteor showers. The Orionid shower has a maximum in activity around October 20 and the Lyrid shower about April 21 (ref. 5).

Averaging of the data for a complete night of observation for all parts of the sky allowed mean emission levels to be obtained (Fig. 1c). Fig. 2a and b show emission rates, at the base of the atmosphere, derived from such averages for the two observing periods. Emission rates (in Rayleighs) are derived from a photometric calibration of the instrument; they are probably good to a factor of 4. Measurements at the "V" wavelength give extinctions of typically 0.15 mag. in the zenith for the Izaña site⁶.

The September and October 1971 data show little significant variation in emission from night to night, having a mean level of about 0.3 Rayleigh.

The April 1972 data show a generally lower emission rate of about 0.1 Rayleigh, with some interesting structure beginning on the night of April 14/15, coinciding with the onset of the Lyrid meteor shower⁵. Two scans recorded near morning twilight on April 15 showed an unusually strong emission of about 0.7 Rayleigh. This declined over the next few nights until another enhancement occurred on April 20/21 corresponding to the time of maximum activity of the Lyrid shower. Unfortunately our data do not extend beyond April 21. It is worth noting that the "enhancements" in late April 1972 merely bring the emission rate up to the September, October 1971 level. In this respect it is not clear whether the emission undergoes an "enhancement" in late April, or is merely at a depressed level in early April. We believe the enhancement to be real, but the difference in ambient emission rates between September, October 1971 and April 1972 may be an artefact of the calibration technique, and modifications to the instrument fore-optics.

Enhancement of the emission at the time of the Lyrid meteor shower suggests that at least part of the atmospheric magnesium is of meteoric origin. No such enhancement occurred during the October 1971 Orionid shower, however.

Arising from the triple $3p^3P-4s^3S$ transition the emission cannot be due to fluorescence excitation, and indeed is observed well into the night when the 90–100 km region of the atmosphere, where most other metallic ions are observed^{7,8}, is completely in shadow.

Radiative recombination of Mg^+ with an electron, the mechanism suggested by Anderson and Barth⁹ governing the daytime balance between Mg and Mg^+ , is the most likely cause of the emission. It would be expected that other MgI lines, such as the other lines of the $3p^3P-4s^3S$ triplet 5172.68 Å and 5167.33 Å, are present with 5183.62 Å. The intercombination line at 4571.1 Å connecting 3P to the ground¹¹ S state should also be present. We know of no observational searches for these emission lines.

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Precambrian Geomagnetic Reversal Stratigraphy

REVERSALS of polarity are encountered in Precambrian rocks. It is therefore important to consider whether geomagnetic field reversals can be a viable stratigraphic tool in the Precambrian.

It is extremely difficult to define a chronologically continuous set of lithologic type sections which represent the entire Precambrian. Not only is there a lack of Precambrian record, due to erosion, metamorphism and coverage by younger rocks, but the fossil record is not as evolutionary and diverse as that used for correlating the Phanerozoic. So there will be gaps in the Precambrian geomagnetic spectrum which will never be filled: this is extremely likely for the interval beyond 2,000 m.y.

Reversals of polarity are a simple binary change. Therefore the exact age of the polarity episode (of whatever time length) must be known if it is to be used for correlation. The only means of determining this is by isotopic dating, and the resolving power achieved so far must be improved upon if this is to be practicable. Dalrymple¹ comments that efforts to extend the potassium-argon reversal time scale beyond 4.5 m.y. ago are probably futile².

The best record of magnetic reversal stratigraphy in pre-Cainozoic rocks will be in thick sedimentary sections, because they represent very long and continuous spans of geomagnetic time³. But there is a basic problem here. In spite of some elegant isotopic studies that have been made on sedimentary rocks^{3–5}, it seems easier to date the time of their metamorphism than the time of their deposition^{6,7}: in addition there is the problem of inherited nuclides from older detritus⁸. An estimate of the maximum and minimum age of a sedimentary sequence can be obtained by the indirect method⁶, which dates the basement underneath and igneous rocks within the sequence. A palaeomagnetic example of this is the Waterberg Redbeds of Southern Africa, which may have been deposited within 100 m.y. (ref. 9)

to 650 m.y. (ref. 10). In that case palaeomagnetic poles from the Redbeds helped in establishing their age⁹ and, when pole paths have been set up for the various continents, they may be of value in the indirect dating of sediments. But the basic uncertainty in sedimentary dating implies that if there were periods of the Precambrian when the reversal frequency was as high as in the Cainozoic, it will be impossible to use individual reversals as a stratigraphic tool, except on a very local scale. If a very long period of constant polarity is observed in a thick sedimentary sequence, as occurred during the late Palaeozoic¹¹, it may be possible to use this for correlation on an intercontinental level. But the isotopic age must still be accurately known.

The best estimate of a Precambrian age will be obtained by isotopic dating of unaltered igneous rocks. This has three implications. First, which isotopic method will give the time of crystallization? Ages by the U/Pb method are up to 10% greater than maximum Rb/Sr or K/Ar ages^{13–15}. For 1,000 m.y. old rocks, Rb/Sr whole rock ages may be over 100 m.y. greater than K/Ar dates^{14,15}. For isotopically homogeneous rocks the Rb/Sr whole rock isochron is the best approximation to the true age of crystallization^{7,8,16}. In addition, because of argon losses¹⁷ there is the question of whether K/Ar ages should be interpreted in terms of an isochron¹⁴, a statistical mean⁶ or the oldest apparent age being taken as a minimum estimate¹⁵.

Second, although the best analytical precision of an isotopic age is from 2 to 5% (refs. 7, 15, 16), the best estimate of the true age is probably nearer 10% (refs. 15, 17). In a rock whose true age is 1,000 m.y., this means we cannot expect to get an analytical precision of this age to better than ± 20 –50 m.y. and a best estimate of the true age to ± 100 m.y. For 2,000 m.y. old rocks the corresponding uncertainty lies between ± 40 and ± 200 m.y. Again, the limited resolving power inherent in a Precambrian age determination implies that it will be impossible to date individual reversals during a period of frequent polarity change. Further, the chances of being able to identify episodes of predominantly constant polarity, which are as long as the 55 m.y. and 60 m.y. intervals found in the Phanerozoic¹¹, are limited up to 1,000 m.y. and probably impossible beyond this time. I thus question Irving's assertion¹¹ that "there are no insurmountable technical difficulties in establishing such a chronology of magnetic intervals [of the order of 50 m.y. in which the geomagnetic field had a characteristic reversal frequency] for the past 2,000 m.y.". Third, although unaltered igneous rocks may give the most reliable age estimates, there are two difficulties in using these alone to set up a Precambrian magnetic stratigraphy. An igneous rock records only a limited amount of geomagnetic time, and this could be a factor of 100 less than the error in resolving the isotopic age of the rock. Watkins¹⁹ implies that it may be possible to use long, continuous sequences of lavas to define the older polarity scale. For a continuous Precambrian lava sequence, however, it is likely that the error in resolving the isotopic age of the top and bottom of the section will be much greater than the length of time represented by the extrusion of the lavas.

There are also practical problems. Showing that the NRM and the polarity are reliable, and can be related to the isotopic ages, is not trivial, because remagnetization may be common in Precambrian rocks²⁰; also the polarity convention can become ambiguous for the interval beyond 2,000 m.y. (refs. 9, 21).

So determinations of the detail of Precambrian magnetic stratigraphy must rely on thick unmetamorphosed sedimentary sequences. Whether these can be used as a stratigraphic tool will depend on the frequency of polarity change. If it is as high as in the Cainozoic there is little hope of being able to correlate individual reversals except on a very local scale, and this may not be a great improvement on lithologic correlations. If very long periods of constant polarity (>100 m.y.) are observed these may provide a means of intercontinental correlation, but

this relies on precise dating of the sedimentary sections. Because of the intrinsic uncertainty in Precambrian isotopic age measurements this is a difficult task: it is unlikely that very long intervals of constant polarity can be isotopically distinguished unless they are about 200 m.y. apart for 1,000 m.y. rocks and about 400 m.y. apart for 2,000 m.y. rocks. Although igneous rocks can be reliably dated it will be unrealistic to use these alone to set up a magnetic stratigraphy because they represent such short intervals of geomagnetic time.

At present, Precambrian pole paths are not firmly established and very little is known about reversal frequency. So it is perhaps unfortunate that Fahrigr, Irving, and Jackson¹⁸ have already defined two Precambrian magnetic intervals based primarily on the mean pole position and reversal frequency shown by sets of igneous rocks. The danger in using reversal frequency recorded in igneous rocks is illustrated by the Mackenzie Magnetic Interval¹⁸. Based on K/Ar ages, the age of the igneous event associated with this interval was originally proposed as about 1,200 m.y. (ref. 22) and has since been modified to 1,250 m.y. (ref. 23). The range in K/Ar ages believed to be reliable (post-1963 data) is from 767–1,330 m.y. (ref. 22), so there is evidence that later disturbing events have caused argon losses and reset ages. A recent Rb/Sr study of one of the dike sets associated with the Mackenzie igneous events suggests a whole rock isochron age of $1,660 \pm 145$ m.y. (ref. 24). Thus there is considerable uncertainty in the isotopic age of the Mackenzie Interval.

Fahrigr *et al.*¹⁸ defined the interval as possessing no reversals, in part based on a section of the Coppermine River volcanics involving "several million years"¹⁸. As I have noted, it may be impossible to discriminate between the isotopic age of the top and bottom of such a continuous Precambrian lava section. Further, I note that mixed polarities are found in sediments from the Yenisey Ridge in Russia²⁵, and that the isotopic age of this sequence is assigned as 930–1,300 m.y.

Mixed polarities are also found in North American rocks of the Belt Series²¹ (isotopic age range¹² from 1,000–1,400 m.y.) and Grand Canyon Series (inferred age²¹ between 1,150–1,400 m.y.). The disturbing question then arises—to which polarity episode does the Mackenzie normal magnetic interval refer, and how effective can it be as an "independent check on lithostratigraphic sequences"¹⁸?

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Gravity Surveys to Delineate African Orogenic Belts

At a discussion meeting (entitled "Evolution of the Precambrian Crust") held at the Royal Society of London, in March 1972, the relationship between ancient cratons and their bordering orogenic belts was discussed in some detail. Particular reference was made to the orogenic belts of Eastern and Southern Africa. For several reasons, the boundaries between the cratons and the orogenic belts are not well defined. This is usually because of lack of detailed ground mapping, the presence of a transition zone between the craton and the orogenic belt, and because of later sedimentary cover.

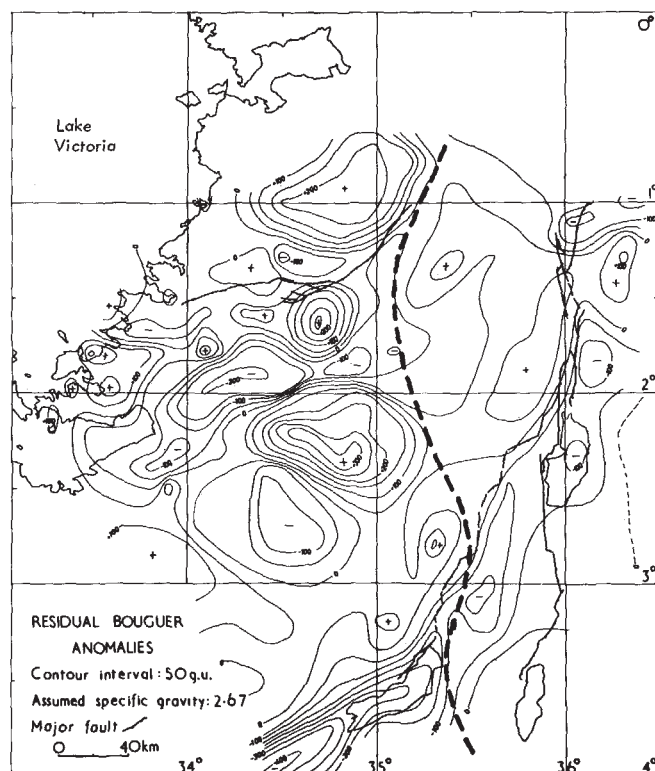


Fig. 1 Residual Bouguer anomalies over the region between Lake Victoria and the Gregory Rift. The north-south trending dashed line represents the boundary between the Tanganyika Shield to the west and the Mozambique Orogenic Belt to the east.

The usefulness of photogeological techniques to "draw tectonic domain maps which are in turn used to recognize and delineate the ancient orogenic belts, making only minimal use of ground mapping" has been demonstrated by Hepworth¹ for the Karmoja region of northeast Uganda. This method, supplemented by detailed ground traverses, has also been applied to a detailed study of the boundary between the Mozambique Orogenic Belt and the Tanganyika Shield, in northern Tanzania^{2,3}. In the Hudson Bay region of Canada, the fixing of the boundary between the Churchill and Superior structural provinces has been aided by detailed

gravity surveys^{4,5}. Here I show the potential usefulness of gravity surveys to delineate the boundaries between ancient cratons and orogenic belts in Africa, using data from East Africa.

In 1968 and 1969, 2,243 measurements of gravity and total intensity magnetic field were made along tracks and roads in northern Tanzania and southern Kenya, as part of a detailed study of the East African Rift System in this region⁶. The survey extended from 33° E to 39° E, and 1° S to 4° S. Fig. 1 is a map of the residual Bouguer anomalies of the part of the region between Lake Victoria and the Gregory Rift. The anomalies were produced by subtracting the broad regional negative Bouguer anomaly associated with the Gregory Rift in Kenya⁷⁻⁹ from the observed Bouguer anomalies. A detailed interpretation of the individual anomalies is given elsewhere¹⁰. The approximately north-south trending dashed line (after Cahen and Snelling¹¹) in Fig. 1, marks the boundary between the Tanganyika Shield to the west and the Mozambique Orogenic Belt to the east. Over the Mozambique Belt there are no large residual anomalies, and in general the gravity field is smooth. In contrast, over the Tanganyika Shield there are several pronounced residual Bouguer anomalies, reflecting the complexity of the ancient granitoid shield. The same observation holds for the ground-level total field magnetic anomalies. This seems to indicate that the residual anomalies are caused by structures which are at least as old as the Mozambique Orogeny (450 to 600 m.y.) and that, if similar structures ever existed further to the east, they have been largely reworked and obliterated by the Mozambique Orogeny. The coincidence of the change in character of the residual Bouguer anomalies and the change from a craton to a mobilized orogenic belt is particularly impressive, and it seems that gravity and magnetic surveys could be usefully employed to delineate the boundary elsewhere. Aeromagnetic profiles across the Mozambique Belt and the neighbouring Tanganyika Shield show a similar change in character (A. G. Green, personal communication). It must be noted, however, that as with the use of photo-geological methods, it is necessary to have some preconception of the style of the geology in the immediate or an analogous area.

Reconnaissance gravity surveys used for this purpose should be particularly useful in places where the boundaries are concealed by Karroo and later formations, as in the case along parts of the Mozambique Belt, though care must be exercised where the cover is likely to be of a heterogeneous nature (for example Tertiary volcanics), as residual Bouguer anomalies may be caused by structures other than the Precambrian basement.

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Holography without Fringes in the Electron Microscope

I REPORT here the successful solution of the phase problem for a negatively stained catalase crystal using diffraction and image plane pictures produced in an electron microscope. The results show the complete wave function, phase as well as amplitude maps, in the microscope image plane. The computational method employed in achieving the solution has been described by Gerchberg and Saxton¹ who demonstrated the technique on general mathematical functions; the method was later successfully applied to mathematical models of magnetic thin films². I have now applied the method to a real biological crystal in the electron microscope.

The object was a beef liver catalase crystal approximately 600 Å thick, negatively stained with an equimolar solution of aluminium and uranyl formate. The object was illuminated with a 100 kV electron beam in a 'Phillips EM-300' electron microscope. Portions of the "selected area" photographs of the image and diffraction planes are shown in Fig. 1. Diffraction plane intensity data were generated by using a series of increasing time exposures. It was thus possible to find the true relative illumination in the diffraction spots, independent of the film and development characteristic distortions. The amplitudes (square root of intensity) of these spots are given in Table 1

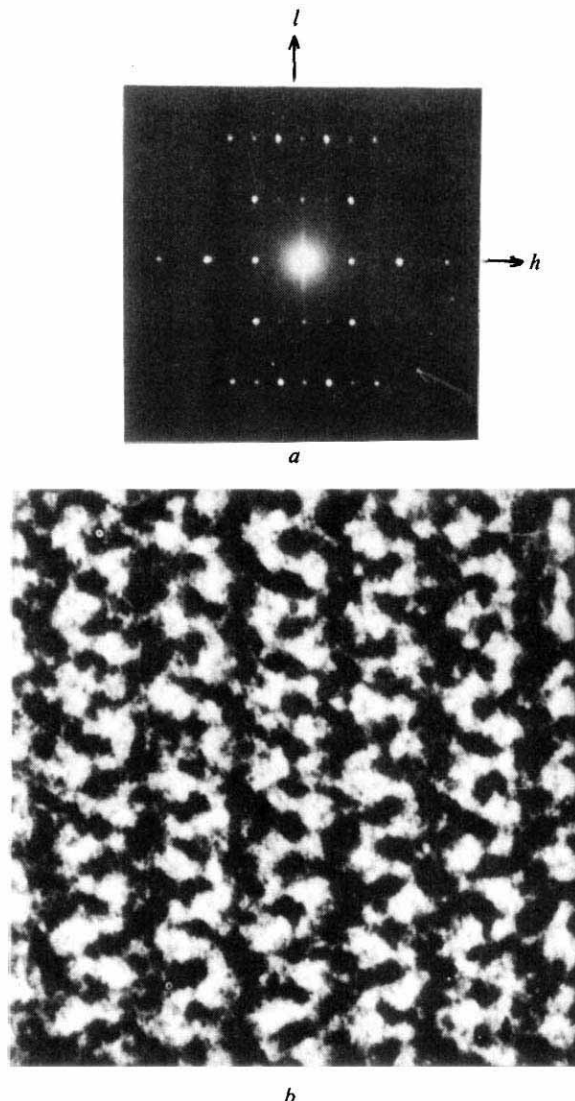


Fig. 1 Negatively stained beef catalase. *a*, Electron diffraction pattern. *b*, Portion of the in-focus electron microscope image. Streak in lower right of *a* is a blemish.

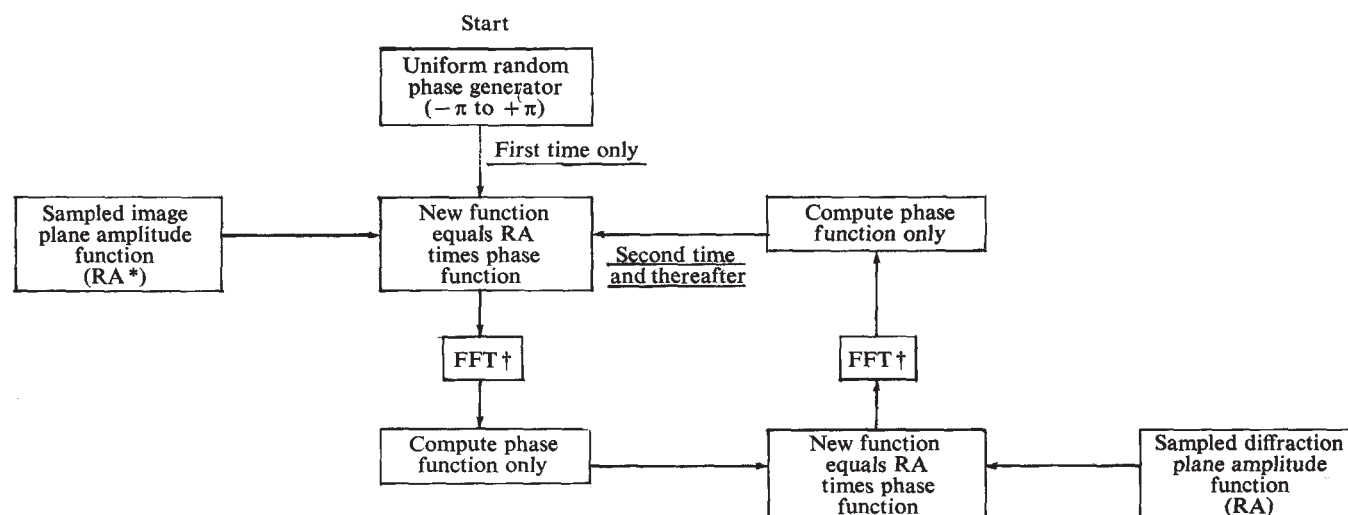


Fig. 2 Computational algorithm used to process data * RA, Reference amplitude. † FFT, Fast Fourier Transform.

together with the amplitudes generated by Fourier transforms of the measured image plane amplitude coupled to the "found" phase function in the image. The computational algorithm which was used to process the data is shown schematically in Fig. 2. The "sampled reference diffraction plane amplitudes" were in an 8 by 16 array ($-4 \leq h \leq 3$, $-8 \leq l \leq 7$) and were the square roots of the measured intensities. Additional weak reflexions were available but were not used. The selected area image contained several thousand unit cells of variable quality. An area containing only four of these cells but showing good detail was chosen and densities determined in an 8 by 16 rectangular grid for each cell, the orientation corresponding with the 8 by 16 sampling of the diffraction plane. The optical densities at corresponding points in the four cells were averaged. As a check, the "averaged cell" was suitably fast Fourier transformed to simulate a sampled optical transform of the

image. The same dominant points as in the electron diffraction pattern were present in the simulated optical transform. The two patterns were recognizably similar, though the relative spot amplitudes varied considerably in the two diffraction pictures. The square root of the optical densities of this "averaged optical density image", normalized, served as the "sampled reference image amplitude" in the algorithm. A large phase spread across the image was not anticipated and so the initial estimate of the phase distribution across the image was chosen from a uniform distribution of numbers between $\pm 1/2$ rather than $\pm \pi$ (see ref. 1 and Fig. 2).

Table 2 shows the history of the error energy (normalized sum squared error) in successive estimates of the complex wave function as the algorithm continued to iterate. (The procedure was terminated after one minute of computer time on the ICL-ATLAS 2 computer which is equivalent to 5 to 10 seconds

Table 1 Amplitudes of Diffraction Pattern Spots Calculated and Measured (Structure Factor Amplitudes)

h,k,l^*	$ F _{\text{meas}}$	$ F _{\text{cal}}$	h,k,l	$ F _{\text{meas}}$	$ F _{\text{cal}}$	h,k,l	$ F _{\text{meas}}$	$ F _{\text{cal}}$	h,k,l	$ F _{\text{meas}}$	$ F _{\text{cal}}$	h,k,l	$ F _{\text{meas}}$	$ F _{\text{cal}}$	h,k,l	$ F _{\text{meas}}$	$ F _{\text{cal}}$
000	102.3	104.5	203	0	0.9	501	0	2.4	102	17.9	16.3	400	25.3	23.5	603	0	1.1
001	8.2	6.9	204	0	1.3	502	0	1.2	103	0	0.7	401	0	1.2	604	0	1.0
002	7.5	6.6	300	0	1.1	503	0	0.3	101	5.2	4.4	402	0	1.9	700	0	1.0
003	0	1.8	301	0	0.5	504	0	0.6	102	15.4	16.3	403	0	0.7	701	0	0.3
001	7.3	8.2	302	9.8	8.6	600	7.3	7.5	103	0	0.6	401	0	1.6	702	0	0.6
002	6.7	5.0	303	0	0.8	601	0	4.0	104	0	0.8	402	0	1.7	703	0	0.6
003	0	2.0	301	0	1.0	602	0	1.0	200	21.4	21.1	403	0	0.4	701	0	1.6
004	0	0.5	302	9.0	8.9	603	0	0.8	201	19.7	19.0	404	0	0.0	702	0	0.8
100	0	1.2	303	0	2.9	601	0	3.8	202	6.3	6.4	500	0	0.3	703	0	1.6
101	5.7	4.0	304	0	0.4	602	0	1.3	203	0	0.7	501	0	1.4	704	0	0.3
102	17.5	15.7	400	22.4	20.9	603	0	0.7	201	19.5	19.2	502	0	2.0	800	0	3.3
103	0	1.9	401	0	1.7	604	0	0.3	202	6.3	6.6	503	0	1.4	801	0	1.6
101	5.2	6.0	402	0	2.0	700	0	1.0	203	0	1.7	501	0	2.6	802	0	0.8
102	16.1	15.5	403	0	1.1	701	0	1.8	204	0	1.0	502	0	0.9	803	0	1.1
103	0	1.6	401	0	1.1	702	0	0.8	300	0	1.0	503	0	1.7	801	0	1.8
104	0	0.2	402	0	0.8	703	0	0.8	301	0	2.7	504	0	1.3	802	0	2.0
200	18.8	18.6	403	0	1.4	701	0	0.8	302	9.8	9.1	600	8.7	9.1	803	0	0.5
201	21.5	17.9	404	0	0.6	702	0	1.2	303	0	2.4	601	0	1.3	804	0	0.8
202	6.7	5.2	500	0	0.6	703	0	0.7	301	0	1.3	602	0	0.9			
203	0	0.9	501	0	0.3	704	0	0.3	302	8.2	8.5	603	0	0.4			
201	18.9	16.6	502	0	0.7	100	0	0.6	303	0	1.8	601	0	2.4			
202	7.5	6.2	503	0	1.3	101	5.9	5.1	304	0	1.9	602	0	1.6			

* - Over coordinate index signifies minus.

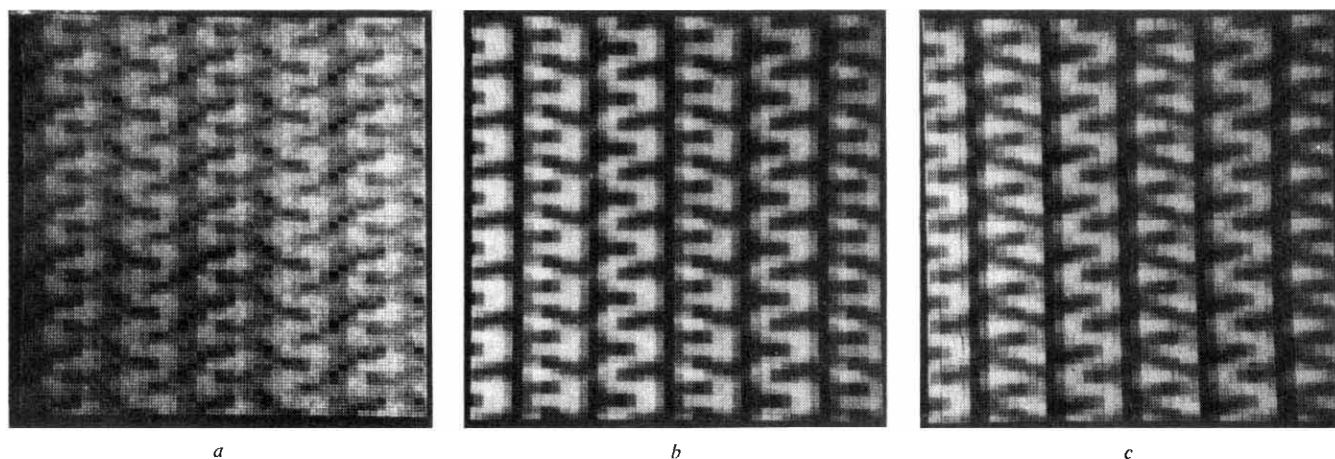


Fig. 3 Input average image data and calculated phase distributions in image. *a*, Averaged image amplitude data used as reference function in processing. *b*, Found or calculated phase distribution across image. *c*, Found or calculated phase distribution across image using a bogus image with no contrast in the computational procedure.

on the IBM 360.) At that point the error energy "visible" by Fourier transform of the actual image (diffraction) amplitudes coupled to their estimated phases was about 1.6% the total picture energy (normalized integrated picture intensity).

Fig. 3a shows a grey level map of the sampled averaged image amplitude function used in processing. Fig. 3b shows a grey level map of the phase found across the image plane. The intensity of illumination for the display of Fig. 3b was linear with phase shift and hence the density on the plate is logarithmic with phase. This "phase contrast" image is, as expected, recognizably similar to the actual image plane picture. The total phase spread across the picture was about 2 rad.

Table 2 Error History of Data Processing

Circuits of algorithm loop *	Error energy (normalized sum square error)
1	39.1
2	11.6
3	5.6
4	3.6
5	3.0
6	2.8
7	2.6
8	2.5
9	2.4
10	2.3
11	2.2
12	2.1
13	2.1
14	2.1
15	2.0
16	2.0
17	2.0

Note: normalized picture energy is 125.8. Picture energy is defined as the picture amplitude function squared and integrated over the entire picture area. Error energy is defined as the squared FFT output in Fig. 2 minus the measured picture amplitude integrated over the entire picture area.

* See Fig. 2.

Although the image plane intensity picture (Fig. 1a) is readily visible to the eye, its measured contrast is quite low, the modulation energy being of the order of 1–2% total picture energy. The modulation is small everywhere in the picture and with the "visible error energy" being about the same size as the image modulation energy it is reasonable to assume that but for the DC or average level of the picture the image detail had little effect in determining the phase distribution found. This explains the apparent missed registration between the amplitude image (Fig. 3a) and the phase contrast image (Fig. 3b). As an experi-

ment processing was repeated, the only difference being the substitution of a blank image for the actual measured image. After the same length of computation the error energy in the estimate was ~1.6% total picture energy and the phase function found differed in only minor respects from the one found previously. It is shown as Fig. 3c.

The method of determining phase using image and diffraction plane pictures has worked well for the electron microscope; there is no reason why it should not do as well in coherent light imaging systems where image and diffraction plane pictures are available. In this way it could serve as an alternative to holographic methods for determining phase. Work at this laboratory is now being undertaken to test the method as a possible aid in X-ray crystallography.

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Peculiarities in the Manifestation of Gaseous-Mud Volcanoes

GASEOUS-MUD volcanoes are one of the most interesting peculiarities of the Earth. They are known in the USSR, in Italy, Rumania, Indonesia, on the coast of the Gulf of Mexico, in Colombia, on the Island of Trinidad, and other areas of the world. The most powerful gaseous-mud volcanoes often not only fail to be inferior to the typically magmatic ones but sometimes surpass them in external effects and in scale. The crater diameters of such typical magmatic volcanoes as Etna, Vesuvius, Stromboli, and Klyuchevaya Sopka amount to 450–900 m. The diameters of major gaseous-mud volcanoes are in the range 300–1,000 m (the Tourgai, Mishovdag, Kalmas, Otmanbozdag and other volcanoes of East Transcaucasia). The heights of the most powerful gaseous-mud volcanoes reach several hundred metres (the Tourgai volcano 400 m, the Akhtarma-Pashali 300 m, and so on). Fig. 1 is an aerial photograph of one of the gaseous-mud volcanic giants, the Tourgai volcano located 13 km to the west of the Caspian Sea;

the crater diameter of this volcano exceeds 0.5 km, whereas the diameter of its base is more than 3 km.

During one eruption of a gaseous-mud volcano the amount of mud breccia thrown out can reach millions of cubic metres whereas the total amount of breccia given off by a single mud volcano is sometimes as high as $(1 \text{ to } 5) \times 10^9 \text{ m}^3$ (the Solokhai, Airantekyan, Tashmardan, Ajiveli and other volcanoes). The total energy of the explosion of the magmatic volcano of Krakatau in 1883 amounted to $2.1 \times 10^{17} \text{ J}$. But the energy released during the eruption of the Makarov gaseous-mud marine volcano, in the Caspian Sea, amounted to $7 \times 10^{16} \text{ J}$; hundreds of millions of cubic metres of hydrocarbon gas that burned out in a fire column 0.5 km high above sea level were thrown out of the volcanic pipe when the volcano erupted in 1958. In this case the fire glow was seen at a distance of up to 200 km. During eruptions of gaseous-mud volcanoes the smoke rises to a height of up to 10–18 km (ref. 1).

So, though many of the gaseous-mud volcanoes usually seem to be slight, the greater of them are violent enough to attract attention and inspire respect.



Fig. 1 The Tourgai gaseous-mud volcano (East Transcaucasia).

Gaseous-mud volcanoes are distinguished by one more interesting feature. It seems that a sharp increase in the number of eruptions (80% of the recorded number of eruptions) takes place when the apse line of the lunar orbit is in the syzygy zone (Fig. 2). The synodic lunar month, with a period of 29.53 day after which a full change of phases occurs, is conventionally divided in two parts having equal durations, a syzygial part and a quadrature part. The line passing through the Earth, the Moon, and the Sun is called the syzygy line. The line connecting the perigee and the apogee of the lunar orbit is called the apse line.

The zones (A, B, C, and D) singled out in Fig. 2 are of the same duration. But their eruption numbers differ sharply from each other. In zones B and D the numbers of eruptions were at a maximum level and almost the same; each zone is characterized by 15 to 17 eruptions of which 8 to 9 eruptions were powerful fiery ones. In zone C the number of eruptions was much lower, only 7 eruptions with only 3 of them being powerful fiery ones. In zone A no eruptions were recorded at all during 23 yr of observations (1948–1971).

Zones A and C on the one hand, and zones B and D on the other hand, may be combined (Fig. 3). Most eruptions—79% of mud eruptions and 85% of powerful fiery eruptions—

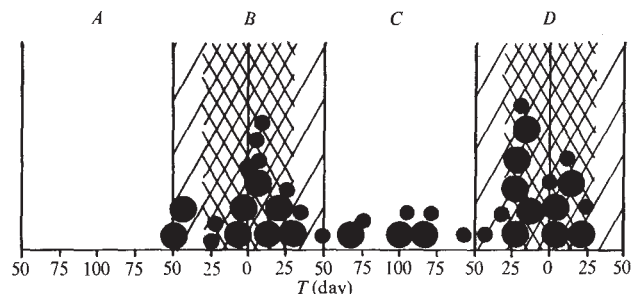


Fig. 2 Eruptions of gaseous-mud volcanoes and the cosmic conditions of the Earth. Large circles denote fiery eruptions, and small circles denote slight mud eruptions (volcanic eruptions of East Transcaucasia and the adjoining part of the Caspian Sea are shown for the period 1948–1970). The time (day) between the moment when the syzygy and apse lines coincide and the eruption day is shown in the horizontal axis. The time during which the apse line is in the syzygy zone is shaded, whereas the time during which the apse line is in the quadrature zone of lunar phases has been left clear. The apse line is in the following zones of lunar phases: A, first quarter; B, new Moon; C, last quarter; D, full Moon.

occurred when the apse line was in the syzygy zone (0–50 day between the moment when the apse and syzygy lines coincide and the observed moment). But when the number of days between the coincidence moment of the apse and syzygy lines and the time of the eruption amounted to 50–100 day there were few eruptions (Table 1). The maximum number of eruptions occurred over a short period (0–30 day) around the interval between the moment of the event and the moment when the apse and syzygy lines coincide.

Table 1 Distribution of the Eruptions of Gaseous-mud Volcanoes of East Transcaucasia and the Adjoining Part of the Caspian Sea during 1948–1971

Eruptions	A										Total
	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	
Fiery	5	5	4	1	2	–	1	–	1	1	20
Mud	4	2	5	2	2	1	–	2	–	1	19
Total	9	7	9	3	4	1	1	2	1	2	39

Note: A is the time interval between the moment when the apse and syzygy lines coincide and the observed event (in day).

The distribution of eruptions with respect to the days of the anomalistic month, reckoned from the moment when the Moon passes the perigee of its orbit to the moment of the

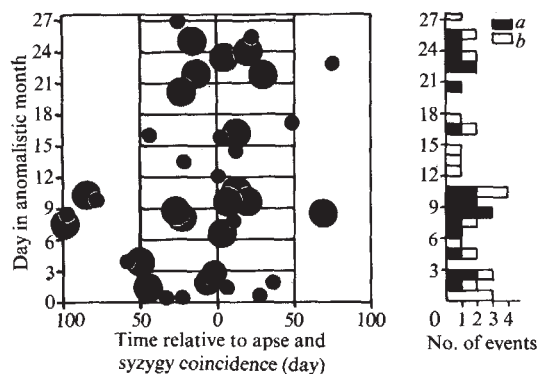


Fig. 3 Distribution of the eruptions of gaseous-mud volcanoes and the cosmic conditions (volcanic eruptions of East Transcaucasia and the adjoining part of the Caspian Sea during 1948–1970). The distribution of the eruptions according to the days of the anomalistic month is shown on the right-hand side. a, Fiery eruptions; b, mud eruptions.

event, does not reveal any selectivity (Fig. 3). The days of the anomalistic month and the apse line taken individually are not of importance; what is significant is the fact that the apse line is in the syzygy zone when the tide-forming forces reach their extreme values.

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New Periodic Close Packings of Identical Spheres

I DESCRIBE here very briefly eleven new periodic close packings of identical spheres. Current literature cites (at most) six, which are: "diamond", β -ZnS ("wurtzite"), Cubic-P, Cubic-I, Cubic-F and hexagonal closest packed (h.c.p.)—the first two having the (same) lowest packing ratios and four-fold coordination and the last two the (same) highest-possible packing ratios and twelve-fold coordination. The two notations (Table 1, columns 1 and 2) should be fairly obvious when related to the "old" packings. The detailed consideration of, for example, high planar densities, "continuous deformation" and spherical voids has been omitted here.

Packing density ("packing ratio") is the total volume of spheres in one unit cell divided by the unit cell's overall volume—analogue densities (planar and linear) exist in 2-D and in 1-dimension. The position of a sphere is that of its centre. A cluster is N spheres all touching ("coordinating") an $(N+1)$ th central sphere. The unit cell is the lattice's "building brick", always a parallelepiped—its shape and size (but not its content) are fully defined by its 3 concurrent (non-coplanar) edges, which are the lattice's 3 periodic or repeat-vectors in space. A unit cell with a sphere at each of its 8 corners and nowhere else contains only one sphere, because all corners

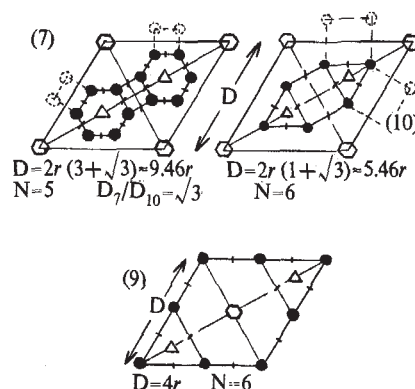


Fig. 1 Three hexagonal packings, lattice triads and hexads shown. Each is a 60° rhombus, $H=2r$ and $\bullet z=0$ (and 1). Packing densities of (7) and (10) are in 2 : 3 ratio.

(and edges and faces) are shared with their immediate neighbours.

Of the seven conditions strictly defining true periodic close packing, only one (apart from all spheres being identical) can be given here: in any one packing the geometric or spatial environment/surroundings of each/every sphere is identical.

In the diagrams the size of each sphere is much reduced relative to the unit cell in which it occurs, and spheres in contact are shown by a short, thick bar across the line joining their centres; all diagrams except Fig. 4 are strict projections. Position coordinates Z are normal to the diagrams and are fractional, their absolute values being H .

Packing (7) with $N=5$ has a packing density even lower than the two cases where $N=4$. Drawing several adjoining unit cells (always recommended) will show that the lattice includes some extremely large spherical voids, radius about $2.86r$, arranged as parallel "tunnels". Note the cluster's very low symmetry. Packing (8) has its sphere centres in any one layer at the corners of close-nested hexagons (like "rabbit-wire") whose edge-length is therefore $2r$. Here $H=2r$. Packing (9) contains two sizes of spherical void, the smaller with radius about $0.53r$. Packing (10) contains three sizes of spherical void and has unexpectedly interesting relationships with (7). Packing

Table 1 Some Critical Features of the 6 Old and 11 New Periodic Close Packings

Name(s) and "(x-y-z) coordination" of each packing. On the extreme left is the number of each packing, used throughout the text and in Tables 1 and 2	"Layer-stacking" or projection-plane sites, using a symmetry- site notation	Coordination number, N , of each sphere (= $x+y+z$)	Point group symmetry of any one cluster (of $N+1$ spheres)	Lattice: centrosymmetric, c or non-centro- symmetric, n
1	2	3	4	5
(1) Cubic (2-0-2) or cubic-tetrahedral or "diamond"	4-ABCD and 3-A ₂ B ₂ C ₂	4	43m	n
(2) Hexag (1-0-3) or β -ZnS or "wurtzite"	6 ₃ -A ₂ B ₂	4	43m	n
(3) Cubic (1-4-1) or cubic-P or cubic primitive	4-A and 3-ABC	6	m3m	c
(4) Cubic (4-0-4) or cubic-I or cubic body-centred. (Also 3(1-3-0-3-1))	4-AB and 3-ABAC	8	m3m	c
(5) Cubic (4-4-4) or cubic-F or cubic face-centred or cubic closest-packed or "c.c.p."	4-AB and 3-ABC	12	m3m	c
(6) Hexag (3-6-3) or hexag close-packed or h.c.p.	6 ₃ -AB	12	6m2	c
(7) Hexag (1-3-1)m (see col. 4)	6-A	5	m	c
(8) Hexag (1-3-1)	6-A	5	6m2	c
(9) Hexag (1-4-1)	6-A	6	mmm	c
(10) Hexag (1-4-1)mm (see col. 4)	6-A	6	mm(2)	c
(11) Orthorhomb (1-5-1) or orth (2-4-1) or orth (1-1-3-1-1)	m-A or mm-A ₂ B ₂ or m-AB	7	mm(2)	c
(12) Hexag (1-6-1)	6-A	8	6/mmm	c
(13) Tetrag (2-4-2)	4 ₁ /4 ₃ -ABCD	8	4m2	n
(14) Tetrag (1-4-4)	4-A ₂ B ₂	9	4mm	c
(15) n-Hexag (1-6-3) (see col. 5)	3-A ₂ B ₂	10	3m	n
(16) c-Hexag (1-6-3) (see col. 5)	3-A ₂ B ₂ A ₂ C ₂	10	3m	c
(17) Tetrag (1-4-0-4-1)—also (2-6-2) etc.	4-AB	10	4/mmm	c

One of the main packing problems is to associate column 3 with column 9B.

(11) is the only orthorhombic lattice, even though, surprisingly, the horizontal planes (normal to the diagram) are square close-packed. There are two sizes of spherical void—short triangular prisms and cubical “cages”. Packing (12) with $H=2r$ consists of layers, each containing closest-packed (hexagonally surrounded) spheres which lie, therefore, at the corners of $2r$ -edged 60° rhombuses. Hence its packing density is $1\frac{1}{2}$ times that of (8). Its low packing density is peculiar in view of its several very high planar densities. Packing (13) contains alternate-direction screw-tetrads (4_1 and 4_3) and, perhaps surprisingly, only the same spherical voids (“ $2r$ -triangular prisms”) as (12). Packing (14) can be derived from Cubic-P—similarly to (11)—by a particular “continuous deformation” process. Packing (15) is non-centrosymmetric. Critics may think that (15), and (16) also, are cases selected

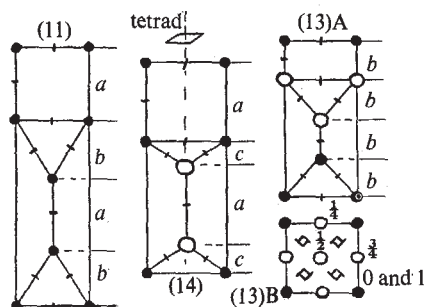


Fig. 2 Three curiously related packings with different N-values. (11) and (14) can be “derived” from known cubic packings. $H=2r=a$, $b=r\sqrt{3}$, $c=r\sqrt{2}$, $N_{11}=7$, $N_{13}=8$, $N_{14}=9$. Except (13) B, $\bullet z=0$ (and 1) and $\circ z=\frac{1}{2}$. In (13) B, showing screw-tetrads (4_1 and 4_3), z -values are fractions of $H_B=4b$.

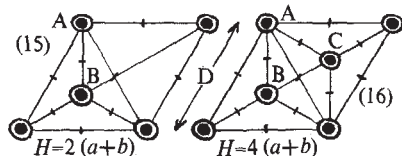


Fig. 3 The two hexagonal (1–6–3) packings, with $D=2r$. The z -values here are absolute, not fractional. (15) is non-centrosymmetric. In both packings $a=2r$ and $b=2r\sqrt{2}/3$. A_{15} sites, $z=0$ (and H) and a . C sites, $z=3(a+b)$ and $4a+3b$. A_{16} sites, $z=0$ (and H) and a and $2(a+b)$ and $3a+2b$. B sites, $z=a+b$ and $2a+b$. Content of (15) is 4, of (16) is 8.

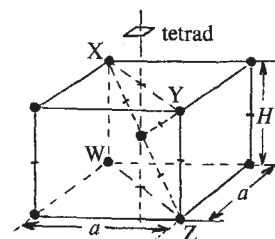


Fig. 4 Perspective view of packing (17). The projection viewed along the tetrad (giving $H=2r$) is deceptively “uninteresting”. $a=r\sqrt{6}$, $H=2r$. Packing density $=(4/3) \times \text{cubic-P}$. WXYZ is one of the two 2-D “h.c.p.” directions.

from a potentially infinite series of hexagonal $A_n B_m C_r$ stacking permutations, but it can be proved (and similarly for tetragonal $A_n B_m$ sequences) that this is not so. Two spherical voids exist, inside the $2r$ -edged triangular prisms and the $2r$ -edged tetrahedra. Packing (16) is centrosymmetric, owing to the introduction of projection-site C, and has the same spherical voids as the simpler (15). Packing (17) is particularly interesting. Its packing density is higher than Cubic-I (the second most dense “old” packing), it contains two planar h.c.p. directions (each parallel to the tetrad), it is the densest possible packing of “close-packed rows” in one direction only, it can be derived by the continuous deformation of Cubic-I and, most surprisingly, by the continuous deformation under “compression” of the highest density Cubic-F.

It is interesting that though some of these packings are non-centrosymmetric, none is holoaxial and/or enantiomorphic and that all seventeen (including the trigonal/hexagonal ones) can be given orthogonal, if unorthodox, unit cells. In all seventeen cases, too, every sphere is in a crystallographically “special position”—on a plane, axis or centre of symmetry—and also the point group symmetry of every cluster is of the same or lower symmetry than that of its lattice; this is not a general law of chemical crystallography, as shown by centrosymmetric triclinic hexamethyl benzene crystals with molecular point group $6/mmm$.

That the ratios $100 \times (\text{packing density}/N)$ vary only between 6.17 and 8.7 and decrease roughly as N increases—with some exceptions, notably (7)—is puzzling, and may be “associated” somehow with the clusters themselves.

I do not imply that other periodic close packings cannot exist, though I suspect (without proof, as yet) that the total number is finite, nor that these general observations are laws. Later I hope to publish the complete version of my findings.

Table 2 Three Dimensional Packing Density Data

No. of packing (see col. 1) and N (col. 3)	Volume of one unit cell, as multiples of r^3	Content of unit cell (=No. of spheres)	Packing density = $4/3 \pi r^3 \times$ col. 8/col. 7 9B is numbered in order of increasing packing density		Some relative packing densities		10B. Multiple of LOWEST packing den- sity, that of (7)
			Precise	Approx.			
			9A		9B	10A	
6	7	8					
(1) 4	$512/3\sqrt{3}$	8	$\pi\sqrt{3}/16$	0.34	2	$(4) \times 1/2$ and $(12) \times (3/4)^2$	1.0496
(2) 4	$256/3\sqrt{3}$	4	$\pi\sqrt{3}/16$	0.34	2	$(4) \times 1/2$ and $(12) \times (3/4)^2$	1.0496
(3) 6	8	1	$\pi/6$	0.52	6	$(5) \times 1/\sqrt{2}$ and $(17) \times 3/4$	1.616
(4) 8	$64/3\sqrt{3}$	2	$\pi\sqrt{3}/8$	0.68	11	$(1) \times 2$	2.099
(5) 12	$16\sqrt{2}$	4	$\pi/3\sqrt{2}$	0.74	13	$(3) \times \sqrt{2}$	2.285
(6) 12	$8\sqrt{2}$	2	$\pi/3\sqrt{2}$	0.74	13	$(3) \times \sqrt{2}$	2.285
(7) 5	$24(3+2\sqrt{3})$	12	$2\pi/3(3+2\sqrt{3})$	0.32	1	$(10) \times 2/3$ and $(11) \times 1/\sqrt{3}$	1.0000
(8) 5	$24\sqrt{3}$	4	$2\pi/9\sqrt{3}$	0.40	3	$(12) \times 2/3$ and $(9) \times 8/9$	1.244
(9) 6	$16\sqrt{3}$	3	$\pi/4\sqrt{3}$	0.45	4	$(12) \times 3/4$ and $(8) \times 9/8$	1.399
(10) 6	$8(3+2\sqrt{3})$	6	$\pi/(3+2\sqrt{3})$	0.48	5	$(11) \times \sqrt{3}/2$ and $(7) \times 3/2$	1.5000
(11) 7	$8(2+\sqrt{3})$	4	$2\pi/3(2+\sqrt{3})$	0.56	7	$(10) \times (4/3)^{1/2}$	1.732
(12) 8	$24\sqrt{3}$	6	$\pi/3\sqrt{3}$	0.60	8	$(9) \times 4/3$ and $(8) \times 3/2$ and $(1) \times (4/3)^2$	1.866
(13) 8	$16\sqrt{3}$	4	$\pi/3\sqrt{3}$	0.60	8	$(9) \times 4/3$ and $(8) \times 3/2$ and $(1) \times (4/3)^2$	1.866
(14) 9	$8(2+\sqrt{2})$	4	$2\pi/3(2+\sqrt{2})$	0.61	9		1.893
(15) 10	$8(\sqrt{2}+3)$	4	$2\pi/3(\sqrt{2}+\sqrt{3})$	0.66	10		2.045
(16) 10	$16(\sqrt{2}+\sqrt{3})$	8	$2\pi/3(\sqrt{2}+\sqrt{3})$	0.66	10		2.045
(17) 10	12	2	$2\pi/9$	0.70	12	$(3) \times 4/3$ and $(8) \times \sqrt{3}$ and $(13) \times 2/\sqrt{3}$	2.156

Note added in proof. I have recently found another (18th) periodic close-packing, related variously to packings (7), (10) and (11). The unit cell is $2r \times 2r \sqrt{3} \times (4r + 2r \sqrt{3})$ and the change from (11)'s $2r$ to $2r \sqrt{3}$ results in changing (11)'s "square close-packed" planes to "h.c.p." planes. Details by column number are: [1] Orthorhomb (2-5-2) or Orth. (2-6-1). [2] m-AB or mm-A₂B₂. [3] 9. [4] mm(2). [5] c. [6] (18)9. [7] $8(3 + 2\sqrt{3})$. [8] 8. [9A] $4\pi/3(3 + 2\sqrt{3}) = 0.64$. [9B] 10. [10A] $(7) \times 2$ and $(10) \times 4/3$. [10B] 2.0000. This 18th packing entails alterations only to column 9B, where all the printed values greater than 9 should be increased by one, so that packings (5) and (6), for example, each become 14.

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BIOLOGICAL SCIENCES

Inhibition of Prostaglandin Synthetase in Brain explains the Anti-pyretic Activity of Paracetamol (4-Acetamidophenol)

INHIBITION of prostaglandin biosynthesis by aspirin-like drugs¹⁻³ has now been confirmed in several systems⁴⁻⁷. The theory¹ that this anti-enzyme action is the basis of the clinical effects of aspirin-like drugs has recently been reviewed⁸⁻¹¹ in detail. One of the few anomalies was that paracetamol (4-acetamidophenol) which has no anti-inflammatory activity, but is analgesic and anti-pyretic¹², was inactive against dog spleen synthetase ($ED_{50} = 100 \mu\text{g ml}^{-1}$). A possible explanation for this discrepancy is that synthetase systems from different regions of the body show different sensitivities to drugs.

Prostaglandins are themselves pyrogenic¹³ and occur in the central nervous system¹⁴. Feldberg *et al.*¹⁵ found that a prostaglandin-like substance appeared in the cerebrospinal fluid (CSF) at the same time as the fever produced by intravenous injections of pyrogen. Paracetamol produced a prompt defervescence, accompanied by a reduction to normal concentrations of the prostaglandin-like substance in the CSF. It seems clear that paracetamol acts centrally as an anti-pyretic, and we have, therefore, investigated the effect of this drug on a prostaglandin synthetase system derived from brain.

Rabbit brain was used, but, in case the effects were due to species differences, confirmatory evidence was obtained on dog brain.

New Zealand white rabbits (or mongrel dogs) of either sex were killed by an overdose of pentobarbitone sodium given intraperitoneally or intravenously. The brain was removed as quickly as possible, cut into pieces with scissors, washed in cold Krebs solution to remove any residual blood, and homogenized in four times its volume of ice cold phosphate buffer (pH 7.4) for 1 min at full speed in a Waring blender. The homogenate was then centrifuged at 100,000g for 1 h to separate the soluble cytoplasmic fraction which contains an NAD⁺-dependent prostaglandin destroying factor. After the supernatant had been discarded pellets were resuspended in phosphate buffer in the proportion (by volume) of 1:3. This suspension (1 ml.) was added to 1 ml. of the buffer containing 20 μg sodium arachidonate, 100 μg reduced glutathione and 10 μg hydroquinone. Drugs tested as inhibitors were added to the reaction mixtures in varying concentrations. Samples were incubated aerobically for 20 min at 37° C with

shaking, after which time the reactions were stopped by heating the tubes in boiling water for 1 min.

Prostaglandin was routinely bioassayed using the rat fundic strip¹⁶, but the identity of the biologically active reaction products was verified by parallel bioassay using the rat fundic strip, rat colon and chick rectum, superfused in series with Krebs solution containing antagonists¹⁷ and by thin layer chromatography (TLC) using the AI and AII systems of Greén and Samuelsson¹⁸. More than 90% of the biological activity eluted from the TLC plates corresponded to the prostaglandin E₂ standard. The potency of the inhibitors of prostaglandin synthesis was calculated from the curves plotted for % inhibition versus log concentration and expressed as the concentration ($\mu\text{g ml}^{-1}$) required to produce 50% inhibition (ID_{50}) of the control synthesis. Brain homogenates were freshly prepared for every experiment.

Zero time activity of the incubation mixture was equivalent to $275 \pm 54 \text{ ng}$ prostaglandin E₂ (mean $\pm$ s.e.). After incubation, there was an average increase in prostaglandin content of $180 \pm 31 \text{ ng ml}^{-1}$.

Table 1 Inhibition of Prostaglandin Formation by Anti-Inflammatory Drugs

	Dog spleen synthetase $ID_{50} \mu\text{g ml}^{-1}$	Rabbit brain synthetase $ID_{50} \mu\text{g ml}^{-1}$
Indomethacin	0.06	1.3
Sodium aspirin	6.6	11.0
4-Acetamidophenol	100.0	14.0

Table 1 shows the ID_{50} concentrations of indomethacin, aspirin and paracetamol against the synthetase derived from rabbit brain compared with their ID_{50} values against the dog spleen enzyme which we reported earlier⁶. Aspirin had similar activities in both systems. However, indomethacin was much less active as an inhibitor of prostaglandin production in brain tissue than in spleen and paracetamol was a more potent inhibitor of brain enzyme than of spleen enzyme. In dog brain also, paracetamol had a similar relatively high potency ($ID_{50} = 12.5 \mu\text{g ml}^{-1}$).

There is a remarkable correlation between the clinical actions of these drugs and their potency against one or other of the enzymes. All three compounds are anti-pyretic (a central action) and all have an inhibitory effect on the brain enzyme in concentrations found in the plasma after therapeutic doses⁶. Both as anti-pyretics and as inhibitors of brain prostaglandin synthetase, the descending order of potency is indomethacin: aspirin: paracetamol^{12,13}. Furthermore, indomethacin is about twelve times more potent than aspirin in both tests. The sensitivity of prostaglandin synthetase derived from brain tissue to paracetamol seems to occur in other species also, for Willis *et al.*¹¹ found that paracetamol inhibited enzymes from mouse and gerbil brain ($ID_{50} = 20 \mu\text{g ml}^{-1}$).

Indomethacin and aspirin are both anti-inflammatory (a peripheral action) and both are active against the spleen enzyme (a peripheral tissue) in therapeutic concentrations. The much higher potency of indomethacin as a synthetase inhibitor both in dog spleen⁶ and in bull seminal vesicles⁵ is also reflected against inflammation in animal models^{5,19} and in man¹². Paracetamol has no anti-inflammatory activity and is not active against the dog spleen enzyme in therapeutic concentrations.

In addition to providing further support for Vane's theory^{1,8}, we believe that our results illustrate the mechanism by which the clinical actions of the aspirin-like drugs are determined by the differential sensitivity of the prostaglandin synthetase systems of the "target" tissues. Thus they support the idea^{1,8} that a study of prostaglandin synthetase systems from different tissues will lead to aspirin-like drugs with a greater specificity of action.

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Lactation following Therapeutic Abortion with Prostaglandin F_{2α}

THERE is little information concerning the effects of the prostaglandins on the mammary gland. Pregnant rats lactate after premature parturition induced by prostaglandin F_{2α} (PGF_{2α})¹, and lactogenesis is induced through the release of prolactin². It has also been shown that PGE₁ decreases the milk-ejection activity of oxytocin in the rabbit and rat^{3,4} whilst in the guinea-pig⁵ the milk-ejection activity of oxytocin is not decreased by PGE₁, PGE₂, PGE_{1α} or PGF_{2α}, which in this species all possess milk-ejection activity *per se*.

Although lactation rarely occurs in women following spontaneous or induced termination of pregnancy before the 4th or 5th month⁶, we observed, during investigations with the intra-uterine infusion of PGF_{2α} for the termination of pregnancy, that a large percentage of women commenced to lactate within 3 days of abortion. Subsequently, a study was made on the incidence of lactation in eighty women receiving PGF_{2α} intra-amniotically for the termination of pregnancy compared with women at a similar stage of pregnancy in whom pregnancy was terminated by surgical means (suction curettage or hysterotomy).

The PGF_{2α} was injected trans-abdominally into the amniotic sac in a dose of 30 mg followed if necessary, at 24 and 42 h, with doses of 15 mg. Before the injection of PGF_{2α}, patients were premedicated with 100 mg of pethidine and two 'Deben-dox' tablets (Wm. S. Merrell: dicyclomine hydrochloride 10 mg, doxylamine succinate 10 mg, pyridoxine hydrochloride

10 mg); during the subsequent interval to abortion, pethidine was used for analgesia and 'Maxolon' (Beecham Research Laboratories: metoclopramide) for the control of nausea and vomiting. All other drugs were excluded due to the possibility of their complicating the reaction to the PGF_{2α}.

Hysterotomy patients received pethidine 100 mg postoperatively for analgesia, whilst patients having a suction curette received no postoperative medication.

Table 1 Effect of Method of Terminating Mid-trimester Pregnancy upon the Incidence of Subsequent Lactation

Method of termination	State of pregnancy	Number of patients	Number lactating	Percentage lactating
Intra-amniotic PGF _{2α}	12-14	17	12	70.6
	15-16	38	32	84.2
	17-20	21	16	76.2
	21-24	4	3	75.0
Hysterotomy	12-16	20	0	0
	17-20	4	1	25.0
Suction curette	11-13	12	0	0

The incidence of lactation observed following the termination of pregnancy by the different methods is shown in Table 1. The high incidence of lactation in the group receiving intra-amniotic PGF_{2α} is significantly different from that in the other groups ($P < 0.001$), although within this group the incidence is not influenced by gestational age.

The data for onset and duration of lactation were based upon the spontaneous chronic expression of milk from the breast following the termination. In nine of the 17 PGF_{2α} patients who failed to lactate, milk was expressed following treatment with oxytocin nasal spray. In those women that lactated following PGF_{2α}-induced termination of pregnancy, the mean interval ($\pm$ s.e.) from the initiation of the PGF_{2α} infusion to the onset of lactation was 71.2 ± 3.4 h, whilst the mean termination-lactation interval was 45.0 ± 3.5 h. Amongst the primigravidae, the mean termination-lactation interval in 12-16 week pregnancies was 49.0 ± 5.8 h but in 17-20 week pregnancies was 27.5 ± 4.2 h. Thus the onset of lactation was earlier in the more advanced pregnancies, although there was no significant difference in the mean induction-abortion intervals. The mean duration of lactation was 6.1 ± 0.6 days and was not influenced by the stage of gestation, but showed a tendency to be longer in primigravidae. Similarly, the incidence of lactation was greater ($P < 0.05$) in primigravidae (43/49 or 87.75%) than in multigravidae (20/31 or 64.5%).

In addition to the above observation, it was noted in five patients that there was a secretion of fluid (clear or cloudy) from the breast within 15-120 min following the second or third infusion of PGF_{2α}, although there was no history of such secretion before the infusion of PGF_{2α} and such secretion did not continue after the miscarriage (and loss of exogenous PGF_{2α} from the amniotic sac).

Samples of milk were obtained from nine PGF_{2α}-termination patients on the 2nd or 3rd day of lactation and were analysed for fat and protein content. The fat content ranged from 0.41 to 5.78 g 100 ml.⁻¹, with a mean ($\pm$ s.e.) content of 2.72 ± 0.61 g 100 ml.⁻¹ and the protein content ranged from 2.68 to 4.95 g 100 ml.⁻¹ with a mean ($\pm$ s.e.) of 3.86 ± 0.36 g 100 ml.⁻¹. Hytten⁷ has examined the composition of normal human milk on successive days of lactation and found 2nd day samples to contain 3.03 ± 0.73 g fat 100 ml.⁻¹ and 4.04 ± 0.65 g protein 100 ml.⁻¹ and 3rd day samples to contain 2.61 ± 0.23 g fat 100 ml.⁻¹ and 1.96 ± 0.11 g protein 100 ml.⁻¹. The milk samples from the PGF_{2α}-termination patients thus appear to be similar to those at an equivalent stage of lactation following a full-term pregnancy.

It seems, therefore, that in the human, PGF_{2α} can induce lactogenesis following the termination of early pregnancy and that PGF_{2α} also possesses milk-ejection activity, although this latter effect may be mediated only through the release of endogenous oxytocin⁸.

It has been suggested⁹ that prostaglandin activation of a receptor linked to adenylyl cyclase in the somatotrope can promote the direct release of growth hormone and that a similar mechanism in the lactotrope may be involved in the hypothalamic inhibition of prolactin release. Such mechanisms would explain the observed¹⁰ reciprocal relationship between the production of growth hormone and prolactin. If, in fact, pituitary release of prolactin is dependent upon prostaglandin withdrawal, it is interesting to speculate concerning the implications of the temporal relationship of the elevated $\text{PGF}_{2\alpha}$ levels in the peripheral plasma of normal pregnant women during the middle trimester, reaching a peak at 17–20 weeks gestational age and thereafter declining¹¹, to the absence of lactation following the termination of pregnancies before the fourth or fifth month⁶, except in those cases where the termination has been induced with prostaglandins.

Further studies are in progress concerning the relation of $\text{PGF}_{2\alpha}$ -induced lactation to changes in peripheral plasma levels of prolactin and placental steroids following the intra-amniotic infusion of $\text{PGF}_{2\alpha}$.

This study was supported by a grant from the National Health and Medical Research Council and the $\text{PGF}_{2\alpha}$ was generously supplied by the Upjohn Company. We are indebted to Dr John McPhillips of the New South Wales Milk Board Research Laboratories for the analysis of the milk samples.

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Loss of Genes coding for Ribosomal RNA in Ageing Brain Cells

ALTHOUGH recent investigations of genetic damage in the ageing process suggest that tissues made up of cells which are continually replaced will not be harmed by mutational events because the most vigorous cell lines are perpetuated selectively, information loss in DNA will be particularly harmful in non-replenishing tissues such as the nervous and muscular systems. Evidence of this effect comes from observations of abnormal mitotic chromosomes in increasing numbers in the cells of regenerating liver in old animals¹, which clearly reflects damage to DNA accumulating during ageing. The importance of chromosomal aberrations in ageing has, however, been discounted somewhat because the exposure of young animals to a dose of X-irradiation sufficient to produce more chromosomal breaks than normally occur during the lifetime of unexposed animals does not shorten the life span of the irradiated animals². Other investigators have suggested an age-dependent increase

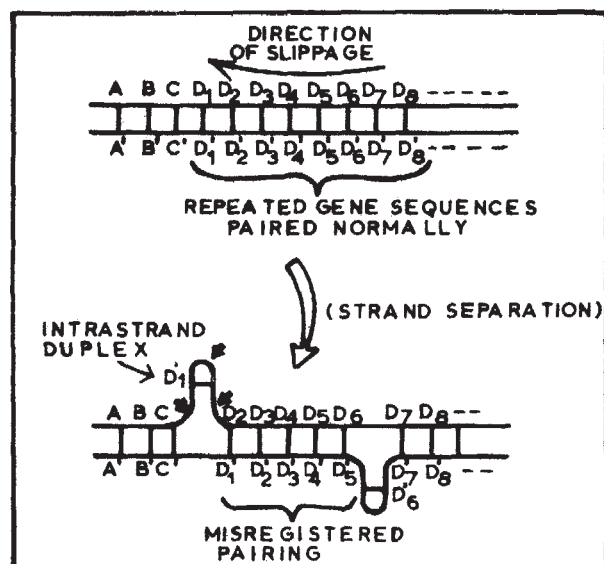


Fig. 1 Postulated hairpin loop structure of tandemly repeated genes. Damage to the unpaired regions (indicated by solid arrows) could not be repaired accurately owing to the improper positioning of the complementary bases. The complementary base is required for accurate base insertion by DNA repair enzymes. The "breathing and slippage" required for the proposed mechanism must involve a longitudinal displacement of at least the length of one rRNA cistron (about 10^4 base pairs): such breathing and displacement normally may be thought to involve much shorter sequences.

in protein crosslinking (reviewed in ref. 3), and there is evidence for the accumulation of single strand scissions in the DNA of ageing mouse neurones⁴.

The occurrence of the latter type of damage, followed by its repair, suggests that a previously undetected kind of DNA alteration involving selective loss of specific regions of the DNA (such as those coding for ribosomal RNA) may be a factor in the reduction of function in non-replenishing tissues during ageing. A postulated mechanism for the selective loss of tandemly duplicated genes⁵ is based on the following considerations: specific DNA regions (those which code for RNA products which possess a high degree of intrastrand complementarity, for example, rRNA and tRNA) will tend to form stable intrastrand duplexes (hairpin loops). Such intrastrand duplex loops would be particularly likely in repeated sequences because further stabilization of such loops as a result of interstrand mis-registered pairings is possible (Fig. 1). The occurrence of damage, such as nicking, to the resultant unpaired regions would lead to erroneous repair because the contralateral strand, properly juxtaposed, is required for accurate base insertion by DNA repair enzymes. Copies of such genes would thus be selectively deleted over extended periods as repeated attacks by nucleases, excision and repair take place.

We report here evidence for selective loss of genes coding for rDNA in DNA from brains of ageing beagles. Tissues were provided by Dr C. Chrisp from dogs raised in the Radiobiology Laboratory colony at the University of California, Davis. Tissues were frozen immediately after death and kept at -20°C until DNA was extracted. Chromatin was prepared by conventional techniques⁶ and DNA was deproteinized by chloroform extractions as described by Marmur⁷. Deproteinization included incubation with self-digested pronase⁸. Native DNA preparations were denatured by treatment with 0.1 N NaOH at 30°C for 30 min, followed by dialysis against $0.1\times\text{SSC}$ (ref. 8) for 15 h. Base denaturation followed by dialysis removed all contaminating RNA.

Hybridization was carried out according to Gillespie and Spiegelman⁹, with the modifications noted below. Just before immobilization on membrane filters, the DNA was subjected to additional denaturation by heating to 90°C for 1 min, followed by rapid cooling and dilution in $6\times\text{SSC}$ to $15\text{ }\mu\text{g/ml}$.

Loading was accomplished by gravity filtration. DNA retention was monitored by measuring the A_{260} before and after filtration. In every case retention was complete.

The unlabelled beagle rRNA used for competition experiments was extracted from purified liver ribosomes by a phenol-SDS procedure⁹. Final purification was accomplished by sucrose density gradient centrifugation. Pooled 18S and 28S components were used.

Because of the relatively large amounts of high specific activity rRNA needed to monitor hybrid saturation levels accurately, a uracil auxotroph of *Saccharomyces cerevisiae* was used as a source of ³H-rRNA. The suitability of this heterologous rRNA for these experiments is based on the extensive interspecific sequence homology of rRNA cistrons reported among numerous eukaryotes including yeast¹⁰⁻¹². To label rRNA, yeast cultures were grown for 5 h in synthetic media containing ³H-uracil (New England Nuclear Corp.). As before, isolation included phenol extraction of purified ribosomes, and pooling of the 18S and 28S fractions obtained from sucrose density gradient centrifugation. To reduce noise, all RNA solutions were passed through membrane filters just before hybridization.

To confirm the suitability of heterologous yeast rRNA in the hybridization-saturation experiments, it was necessary to determine whether the yeast rRNA is specifically bound to DNA sites complementary to homologous (dog) rRNA. The validity of this procedure was demonstrated in the competition

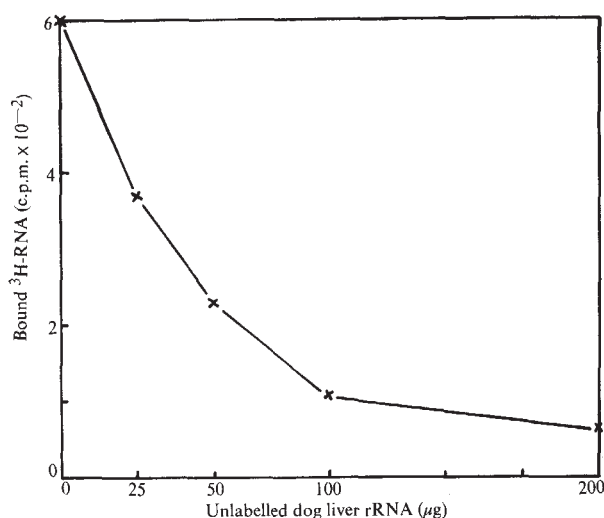


Fig. 2 Competition between unlabelled beagle liver rRNA and yeast ³H-rRNA for hybridization to beagle DNA. Filters containing 25 μg DNA were incubated at 62° C for 15 h with 25 μg yeast ³H-rRNA in the presence of increasing quantities of unlabelled beagle rRNA as indicated. The reaction was carried out in sealed vials containing 0.75 ml. 2SSC and 0.1% SDS. The background counts (c.p.m. retained by blank filters) were subtracted.

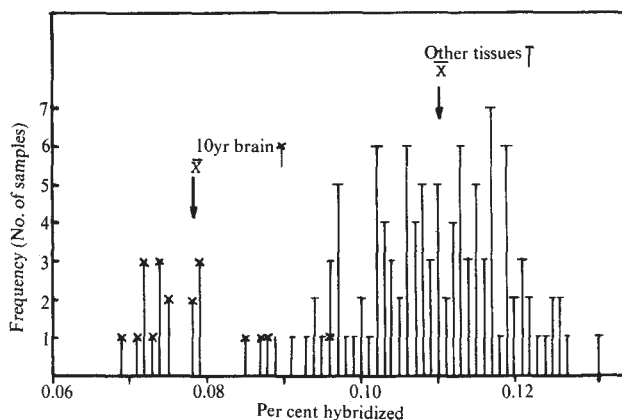


Fig. 3 Frequency distribution of hybridization values. DNA from the tissues listed in Table 1 was hybridized with ³H-rRNA as described in Fig. 1. The specific activity of the rRNA was 21.8×10^3 c.p.m./μg. Control experiments using filters loaded with the same quantity of *E. coli* DNA (Sigma Chem. Co.) and incubated simultaneously with ³H-rRNA of the same preparation retained radioactivity not significantly differing from blank filters. Hybrid saturation experiments in which the input RNA : DNA ratio was varied from 0 to 8 showed that a plateau was reached at an input ratio of about 0.5 under these hybridization conditions. In order to negate the possibility that differences might simply reflect significant (and selective) losses of DNA from the filters during hybridization, filters were extracted after hybridization, washing, and RNAase treatment. Based on the A_{260} in the extracted material, no measurable differences were observed.

experiment illustrated in Fig. 2. In the presence of an eight-fold excess of unlabelled dog rRNA, hybridization of yeast ³H-rRNA was reduced to about 10% of the level observed in the absence of competitor.

Because of the lack of complete interspecific sequence homology of rDNAs of these two species, the hybrid saturation level measured represents a minimum value. But the hybridization levels presented in Fig. 3 and Table 1 correspond to the higher of the values reported for mammalian rRNA-DNA hybrids, which range from 0.02% to 0.15% (refs. 13-16). Minor differences in hybridization conditions may be responsible. Alternatively, the results may mean that a comparatively large fraction of the dog genome codes for rRNA and that these nucleotide sequences are very similar to those of yeast. After hybridization, all filters were incubated with pancreatic RNAase (20 μg/ml. for 1 h at 27° C). Therefore, the observed level of binding cannot be a consequence of the retention of appreciable non-hybridized regions of RNA. When the RNAase step was omitted, a five-fold increase in c.p.m. bound was observed (not shown).

The key observation (Fig. 3 and Table 1) is that the mean hybridization level of 10-yr brain DNA is 29% less than that of the other tissues examined. Previous studies have shown that, except for the occurrence of gene amplification in certain oocytes^{17,18}, the proportion of rDNA in various tissues of a

Table 1 Range and Mean Hybridization Values for DNA from Various Beagle Tissues

Source of DNA, tissue and age	Number of measurements (No. of filters)	Number of animals used	Hybridization range, %		Average % hybridized (RNA:DNA × 100)
			min.	max.	
Brain, 10 yr	20	2	0.069	0.096	0.077
Liver, 10 yr	20	2	0.091	0.124	0.110
Brain, 4 yr	10	1	0.096	0.119	0.107
Liver, 4 yr	10	1	0.095	0.117	0.107
Spleen, 4 yr	10	1	0.093	0.112	0.102
Brain, 1 yr	20	2	0.110	0.131	0.117
Liver, 1 yr	20	2	0.084	0.122	0.106
Spleen, 1 yr	20	2	0.097	0.127	0.110

The frequency distribution of these data is shown in Fig. 2. Other details are given in the legend to Fig. 2. To negate the effect of regional differences in brain tissue, brain DNA was prepared from two separate portions of cortical tissue from each animal. Within each of the specified age groups all the different tissues were taken from the same animal (or the same two animals).

given vertebrate species, is approximately the same¹⁹. The rDNA content of senescent tissues, however, has not been studied before.

The results are most readily interpreted as a selective loss of rDNA during ageing, although less selective kinds of damage to the genetic material are not excluded by our experiments. In evaluating the significance of the findings reported here, the heterogeneity of brain tissue should be kept in mind. This organ consists of both "reversibly postmitotic" glial cells²⁰ and completely postmitotic neurones. We have not attempted to separate these cell types before extracting the DNA. If, however, the rDNA deficiency resides in just one of these cell types (for example neurones) the loss must be even greater in these cells than our measurements indicate.

It is difficult to imagine that such a substantial loss of rDNA as reported here would have no effect on function of these animals, whether the mechanism of deletion is as postulated or otherwise. It should also be noted that the old dogs were not of maximal age: the greatest attained age of certain strains (such as Pekinese) is about 20 yr. Thus, a 30% loss at 10 yr suggests an even more substantial loss in very old animals, possibly sufficient to reduce function to that minimum compatible with life.

These findings may also be relevant to changes in ova during the ageing of the mother²¹. During meiosis the level of restitution of rDNA dosage in different eggs may differ either as a result of asymmetric crossover or gene amplification of the type observed in other forms. A different mechanism for gene amplification would result if a nick occurred in the unlooped segment opposite a loop, and if this were followed by insertion of a segment complementary to the loop (Fig. 1). If mechanisms serving to restore rDNA dosage are operative only during meiosis or egg maturation, this may represent a special rejuvenatory function of sexual processes, and at the same time provide an evolutionary basis for the selection of highly vigorous offspring within the ovary.

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An EEG Experiment Aimed Toward Identifying Dyslexic Children

THE purposes of the experiment were to search for spectral features for identifying dyslexic children, to demonstrate the statistical significance of any such features, and to start a data base that could ultimately result in a reliable discriminant function for the early detection of reading disabilities.

Twelve Caucasian dyslexic children (10 boys, 2 girls, aged 9–18 years, mean 11.5 years) were selected and 13 controls were age and sex-matched (11 boys, 2 girls, aged 7–16 years, mean 11.6 years). Their electroencephalograms (EEGs) were monitored for 10-second periods during five situations: rest, eyes closed; attentive, eyes open; performing mental arithmetic; reading word lists; and reading text. Electrodes were placed according to the International 10-20 system¹ and the following channels were standardized for all testing: F3-T3, F4-T4 (fronto-temporal), F3-P3, F4-P4 (fronto-parietal), P3-O1, P4-O2 (parieto-occipital), O1-T3, O2-T4 (occipito-temporal). Thirteen sex-matched normal children were used as controls.

Spectral analysis of the digitized version of the analogue recordings was carried out. Auto-spectral estimates were derived for the frequency band from 1 to 32 Hz with a resolution of 1 Hz, and cross-spectral estimates of coherence were determined for each pair of traces. These estimates were normalized and used as input to a stepwise discriminant analysis programme^{2–4}, to select the EEG parameters most disparate between the dyslexic and normal groups. The programme successfully discriminated between the two groups during all five test situations. The best results were obtained from the rest, eyes closed and the reading text situations and we present primarily these results.

During the rest, eyes closed phase the most disparate activity appeared in the parieto-occipital region. The dyslexic children on the average had more energy in the 3–7 Hz band and the 16–32 Hz band; the normal children had more energy in the 9 to 14 Hz band. Fig. 1 is a logarithmic plot of the average P3-O1 normalized spectrum for each group.

Spectra were normalized as follows

$$S_{Ni} = \frac{S_i \Delta_f}{\sum_{j=1}^{32} S_j \Delta_f} \quad i, j = 1, \dots, 32 \text{ Hz}$$

where S_i = spectral estimate at index i and $\Delta_f = 1 \text{ Hz}$.

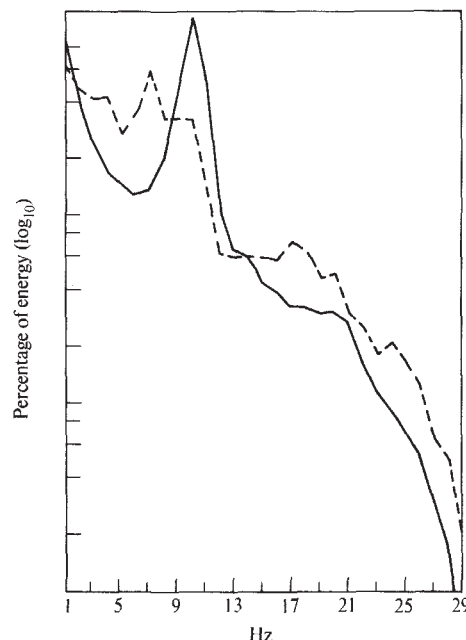


Fig. 1 P3-O1 auto-spectral averages for rest, eyes closed. —, Normal; ---, dyslexic.

Table 1 Nine Discriminating Features Selected for Each Situation

Situation	Auto-spectra		Coherence	
	N	D	N	D
Rest	P3-O1 (band 3)	P3-O1 (bands 2, 4, 5)	P3O1/P4O2 (band 3)	O1T3/T3F3 (bands 2, 4)
Eyes closed	T3-F3 (band 1)	T3-F3 (band 2)		
Attentive	P3-O1 (band 3)	P3-O1 (bands 2, 4, 5)	P3O1/P4O2 (band 3)	O1T3/T3F3 (bands 2, 4)
Eyes open	T3-F3 (band 1)	T3-F3 (band 2)		
Performing mental arithmetic	P3-O1 (band 3)	P3-O1 (band 2)	P3O1/P4O2 (bands 2, 3)	O1T3/T3F3 (bands 2, 3, 4)
	T3-F3 (band 1)	T3-F3 (band 2)		
Reading word lists	P3-O1 (band 3)	T3-F3 (band 2)	P3O1/P4O2 (bands 2, 3)	O2T4/T4F4 (bands 2, 3, 4)
	T3-F3 (bands 4, 5)			
Reading text	P3-O1 (band 3)	T3-F3 (band 2)	P3O1/P4O2 (bands 2, 3)	O2T4/T4F4 (bands 2, 3, 4)
	T3-F3 (bands 4, 5)			

N, Normals > dyslexics (mean value). D, Dyslexics > normal (mean value).

The plot was generated to establish appropriate "banding" regions for data reduction purposes. By itself it gives no indication of significance (Table 3). During reading, auto-spectral signatures played a less discriminating role than during rest; more important were the coherences between regions O2T4/T4F4 and regions P3O1/P4O2 (symmetrical across the midline). The former were higher for dyslexics and the latter higher for normals.

Initially we thought that reading might elicit the most disparate features, since it is here that the dyslexics manifest their primary difficulty. However, we were able to classify the rest (eyes closed) cases most reliably. It seems that, during any uniformly constrained situation, the EEGs of two different groups will appear more alike than when the constraints are removed. Individuals in deep sleep have a sameness in their EEGs, and EEGs tend to increase in frequency and the various channels tend to desynchronize during a mental task. Electrodes near the eyes were used to obtain simultaneous recordings of lateral and up-down eye movements. At first we chose classic clinical bands and, when analysis pointed to the parieto-occipital region, we re-examined these data (P3-O1) in 1-Hz bands from 1 to 32 Hz. There were notable auto-spectral signature differences between groups (Fig. 1) and these differences could best be displayed by banding the data as follows: band 1: 1 to 2 Hz; band 2: 3 to 7 Hz; band 3: 9 to 14 Hz; band 4: 16 to 22 Hz; band 5: 23 to 32 Hz. After this standardization, the initial computations were repeated.

There were 275 variables to consider (10 auto-spectra and 45 coherence functions in 5 bands). There was much disparity between groups in the eye-channel spectra. Because we did not know whether we were measuring a cause or an effect, we eliminated these items in the discrimination, thus reducing the total number of variables to 152. The data seemed highly correlated so that various different features could have been selected as discriminators; there was a consistent pattern in the coherence functions. Within the same hemisphere, coherences between leads were higher in dyslexics than in normals on the average, and coherences between symmetrical regions across the midline of the head tended to be higher in normals. Table 1 gives the discriminating features selected for each situation. In each situation there are nine variables comprised of two auto-spectral channels (P3-O1 and T3-F3), and two coherence channels O1T3/T3F3 and P3O1/P4O2. In the reading tests the coherence O2T4/T4F4 in the right hemisphere proved to be a better discriminator than O1T3/T3F3 in the left (Table 1).

For each of the five phases the null hypothesis is: the mean of the nine component dyslexic vectors is equal to the mean of the normal vectors. On the basis of the pooled data, any one of the five tests could be used to discriminate between the groups. A more meaningful statistic was obtained by averaging the results for each child and taking each subject as a single data point in the sample space. Table 2 lists the *F* statistic with degrees of freedom for each situation where a child constitutes such a data point. The degrees of freedom differ between the first three phases and the last two because we could not obtain artefact-free recordings from one of the

children in each of the first three situations. For the rest, eyes closed situation we rejected the chances of the dyslexic mean equalling the normal mean in the population at the 1% level. Table 3 lists the *F* statistic for each of the selected nine variables, for the rest (eyes closed) situation. For the O1T3/T3F3 band 4 variable we rejected the null hypothesis at the 0.1% level. This rejection is also better than the 0.5% level for variable P3-O1 band 2.

Tables 2 and 3 provide some quantitative assessment of the experiment. Although the mathematics for demonstrating significance have not yet been developed for stepwise discriminant analysis (W. J. Dixon, personal communication), the discriminant analysis can be rerun on a random subset of the original data (152 variables), for example, half the dyslexics and half the normals (training subset). The discriminating function obtained can be used to test the other half of the subjects (testing subset). If we classify those subjects whose data were not used to determine the optimum variables with accuracy better than chance, we have some confidence in the homogeneity of our experiment. 89% of the testing subset were correctly classified after selection of the best three variables (rest, eyes closed). In addition, 69% of the testing subset was correctly classified for the reading situation. This indicates that, using the features of a random half of the total subjects and treating the other half as unknowns, we are able to classify appreciably better than by chance alone.

Another technique for providing confidence, where expected *F* ratios of single variables between groups are unknown, is to scramble the data into two pseudogroups and run the stepwise discrimination again. When we did this, and looked for disparate features among 152 variables, we classified only 79% correctly as opposed to 93% for the real groups (rest,

Table 2 *F* Statistic of the Two Groups Using Individual Subjects

	<i>F</i> Statistic with degrees of freedom	α
Rest (eyes closed)	4.41 (9, 14)	< 1%
Rest (eyes open)	2.87 (9, 14)	< 5%
Arithmetic	1.65 (9, 14)	> 10%
Reading (word lists)	2.28 (9, 15)	< 10%
Reading (text)	3.53 (9, 15)	< 2.5%

Table 3 *F* Statistic for the Selected Rest Situation Variables

	<i>F</i> Statistic with d.f. (1, 22)	α
F3-T3 band 1	6.87	< 2.5%
F3-T3 band 2	5.37	< 5%
P3-O1 band 2	11.65	< 0.5%
P3-O1 band 3	3.02	< 10%
P3-O1 band 4	6.87	< 2.5%
P3-O1 band 5	7.94	< 1%
P3O1/P4O2 band 3	1.93	> 10%
O1T3/T3F3 band 2	6.30	< 2.5%
O1T3/T3F3 band 4	20.60	< 0.1%

eyes closed), which suggests that the dyslexic disparities are greater than what we might find by chance alone.

The EEG spectra of dyslexic children seem to have some prominent differences from those of normal children, the most recurring of these being higher theta-band activity and, during mental tasks, higher coherence between regions in the same hemisphere. We are continuing testing to obtain more data for possible prediction.

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Physiology of Grain Filling in Barley

THE relative importance of various photosynthetic organs as suppliers of assimilates to developing grain in barley and as determinants of the yield of grain per ear has attracted much attention. It has been shown that the major contributions are made by the flag leaves and photosynthetic tissues of the ears themselves^{1,2}; little or no information is available regarding the relative contributions of the various organs to the individual grain within the ear; furthermore there is little understanding of the mechanisms by which differences in growth rates between grains develop.

Study of the growth rates of individual grain within barley ears has shown that there was a strong correlation between the final weight of any grain and the length of the awn of the lemma subtending that grain³ (Fig. 1). This strongly suggests that an awn supplies assimilate predominantly to the grain which it subtends, and that differences in awn area are important in causing the observed differences in growth rates between grain. These hypotheses have been tested in an experiment in which ¹⁴CO₂ was applied to either the flag leaves or individual awns of barley ears at different times after anthesis and the distribution of labelled assimilate to the individual grain followed.

Seed of the barley cultivar Maris Baldric was sown in pots of John Innes Compost (No. 2) and the plants were grown in a cool greenhouse. Shortly after anthesis thirty-two plants, each with the same number of fertile tillers and fertile spikelets per main shoot ear and at comparable stages of development,

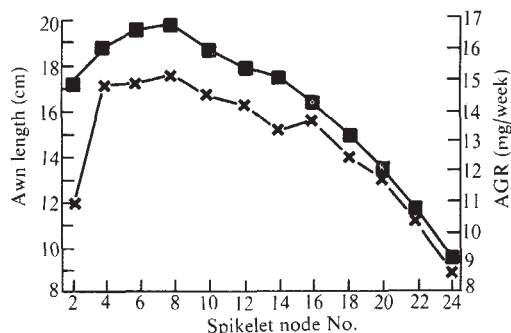


Fig. 1 Mean awn lengths at each even numbered spikelet node and the mean absolute growth rates (AGR) of grain at similar nodes from seven to twenty-one days after anthesis. ■, Awn length; ×, AGR.

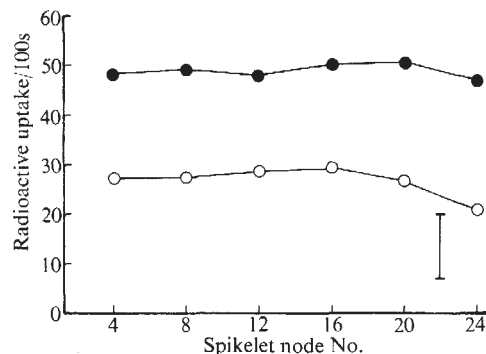


Fig. 2 The distribution of radioactive assimilate between grain at even-numbered spikelet nodes following the application of ¹⁴CO₂ to the flag leaf seven days after anthesis (○) and twenty-one days after anthesis (●). Bar, LSD at 5%.

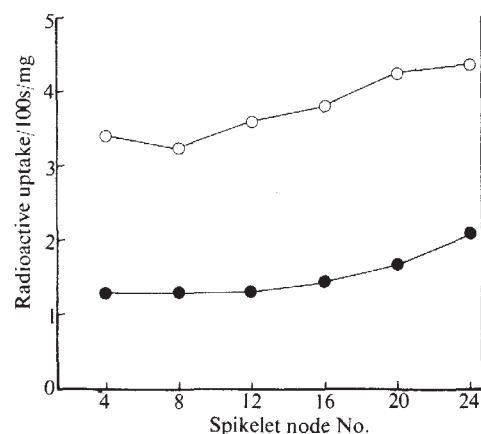


Fig. 3 The specific activity of grain at even numbered spikelet nodes following the application of ¹⁴CO₂ to the flag leaf seven days after anthesis (○) and twenty-one days after anthesis (●).

were selected for treatment; ¹⁴CO₂ was applied to the flag leaves of the main shoots of eight plants and to the awns subtending spikelet 10 (numbered from the basal fertile spikelet upwards) of another eight plants, seven or twenty-one days following anthesis. In each case the organ to be treated was enclosed in a clear, sealed glass cylinder to which ¹⁴CO₂ was introduced. After a treatment period of 3.5 h, the ears were immediately oven dried, and the individual grain weights at even numbered spikelet nodes determined. The radioactivity in selected grain was assayed with an end-window counter using a technique based upon that of O'Brien and Wardlaw⁴. As the total amount of radioactivity translocated to the grain varied between replicates, the data were subjected to a square root transformation before statistical analysis.

Following both treatments of the flag leaf, the absolute amounts of radioactivity which became distributed between the different grain were broadly similar (Fig. 2), so that the lighter apically situated grain contained more radioactivity per unit dry matter (Fig. 3). In contrast, the substantial quantities of ¹⁴CO₂ assimilated by the awns did not become generally distributed within the ear and virtually all the labelled material was retained in the grain subtended by the treated awn (Table 1).

Table 1 Distribution of ¹⁴C after Application to the Awn Subtending Spikelet 10

	T ₁	T ₂
% Retention by spikelet 10	94.2	99.6
% Moved up the ear	5.0	0.3
% Moved down the ear	0.8	0.1

The table shows distribution of radioactive assimilate between even numbered grains of the ear following the application of ¹⁴CO₂ to the awn subtending spikelet 10 seven days after anthesis (T₁) and twenty-one days after anthesis (T₂). Figures are means of eight plants.

The results show clearly that differences in growth rates between grains are unlikely to arise because of a greater supply of flag leaf assimilates to the more rapidly growing grain. A more likely explanation is that they are due to the different amount of assimilate supplied by each photosynthesizing awn, the area of which is a major factor in determining the amount. The fact that $^{14}\text{CO}_2$ assimilated by the awn goes primarily to the grain which it subtends supports this reasoning.

The above findings are of considerable applied interest, since it is likely that the size, duration and photosynthetic efficiency of the awns will now be important criteria for selection in any breeding programme for increased yield in barley.

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Role of Reactions of Molybdenum Compounds with Hydrazine in Nitrogen Fixation

THE enzyme nitrogenase catalyses the reaction:



Nitrogenase is a metalloenzyme containing iron and molybdenum both of which are essential for catalytic activity. Reduction of nitrogen is thought to proceed in two-electron steps via bound intermediates at binuclear molybdenum and iron centres with the oxidation state of molybdenum changing possibly from 3+ to 6+ (refs. 1 and 2). Shilov *et al.*³ suggested that the 3+ oxidation state of molybdenum participated in the catalytic reduction of dinitrogen to hydrazine in an aqueous system at pH > 7 containing initially molybdate (VI), vanadium (II) or titanium (III), and magnesium (II). In view of this work and evidence⁴ that bound hydrazine is an intermediate in biological nitrogen fixation we have studied the reactions of hydrazine with binuclear molybdenum (III) and (V) in the compounds μ -dioxo-bis[triaquochloromolybdenum(III)], (I), and caesium μ -dioxo-bis[aquodichloro-oxomolybdenum(V)], (II).

Hydrazine hydrate was added dropwise at room temperature to solid samples of compounds (I) and (II) (Fig. 1). After a few minutes solid products, (III) and (V) respectively, were washed with a little cold water and dried *in vacuo*. Compounds (III) and

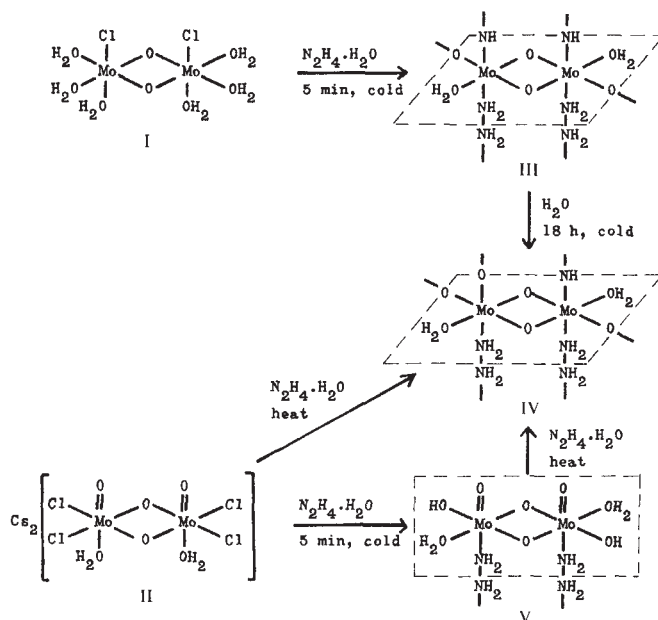


Fig. 1 Reaction scheme for production of molybdenum-hydrazine complexes. Repeating units are in boxes. Note that $-\text{NH}-\text{Mo}$, $-\text{NH}_2-\text{NH}_2-\text{Mo}$, and $-\text{O}-\text{Mo}$ represent bridging structures. Each bridging group counts one-half per molybdenum in arriving at the formula of the repeating unit. Lattice water (Table 1) is not included.

(V) were further treated with cold and hot water giving identical products (IV). Reactions are summarized in Fig. 1. The compositions of all compounds were determined by elementary analysis, water by thermogravimetric analysis, and reducing equivalents by iodate titration using Andrews's procedure ($\text{IO}_3^- \equiv 4\text{e}^-$)⁵. Characteristic chemical groups were identified by infrared spectroscopy. Apparent magnetic moments at room temperature (approximately 293 K) were determined by the Gouy method. Results are given in Table 1.

Proposed structures are shown in Fig. 1. Compounds (I) and (II) have been discussed elsewhere^{6,7}. We suggest that compounds (III)–(V) are polymeric with repeating units, having structures consistent with the stoichiometries, physical measurements, an assumed molybdenum coordination number of six, and the requirement of overall charge neutrality.

Compounds (I) and (II) contain the dioxo-bridged MoO_2Mo group, vibrations of which give strong infrared bands at ca. 700 cm^{-1} (refs. 6 and 7). Bands in this region are observed for all our compounds (Table 1) showing that the MoO_2Mo group persists through all the reactions with hydrazine. The MoO_2Mo vibration moves to higher wave numbers when compound (I) reacts with hydrazine; this indicates⁶ oxidation of molybdenum (III) by hydrazine. In compounds (III)–(V) the presence of a monoxo-bridged MoOMo group is indicated by a band at 850 cm^{-1} (ref. 7). In compound (II) the presence of an MoO

Table 1 Properties of Molybdenum Complexes

Compound	Analysis	TGA *	Iodate titration †	MoO	Infrared spectrum ‡	MoO ₂ Mo	NN	Magnetic moment §
I	$\text{Mo}_2\text{O}_2\text{Cl}_2(\text{H}_2\text{O})_6$	$6\text{H}_2\text{O} > 120^\circ$	6e^-	—	—	670 s	—	0.44
II	$\text{Cs}_2[\text{Mo}_2\text{O}_4\text{Cl}_4(\text{H}_2\text{O})_2]$	$2\text{H}_2\text{O} > 130^\circ$	2e^-	960 vs	—	725 s	—	0.38
III	$\text{H}_{11}\text{Mo}_2\text{N}_3\text{O}_6$	$1\text{H}_2\text{O} > 60^\circ$	8e^-	—	850 m	730 s	940 m	0.40
IV	$\text{H}_{10.5}\text{Mo}_2\text{N}_2.5\text{O}_6.5$	$1\text{H}_2\text{O} > 70^\circ$	8e^-	—	850 m	740 s	940 m	0.35
V	$\text{H}_{12}\text{Mo}_2\text{N}_2\text{O}_9$	$1\text{H}_2\text{O} > 50^\circ$	6e^-	953 vs	—	740 s	940 m	0.43

* Thermogravimetric analysis with the number of water molecules per formula unit expelled and the temperature at which loss of water commenced.

† Number of reducing equivalents per formula unit.

‡ Wave numbers/ cm^{-1} of bands assigned to vibrations of the groups listed (vs, very strong; s, strong; m, medium). For compounds (III)–(V) an Mo–N stretching vibration was observed at about 450 cm^{-1} .

§ Bohr magnetons at ca. 20°C .

group with terminal oxygen, that is oxygen bound to only one molybdenum, is indicated by a band at 950 cm^{-1} (ref. 8). The low magnetic moments of the complexes are consistent with bi- or poly-nuclear structures with magnetic interactions between adjacent molybdenums⁸.

According to our thermogravimetric analyses (Table 1) compounds (III)–(V) contain one molecule of lattice water per formula unit. Lattice water is expelled at a lower temperature than coordinated water (compare with compounds (I) and (II))^{6,9}. At higher temperatures general decomposition of compounds (III)–(V) occurred so we could not determine coordinated water.

Iodate titrations (see below) show that complexes (III)–(V) have $\text{Mo} : \text{N}_2\text{H}_4 = 2 : 1$. That the hydrazine acts as a bridging group between molybdenum atoms is indicated by comparison of the infrared spectra of our complexes with hydrazine complexes of known structure¹⁰. In particular the N–N vibration is shifted from the value 876 cm^{-1} in hydrazine to 940 cm^{-1} in the range ($948\text{--}985\text{ cm}^{-1}$) found for complexes containing bridging hydrazine¹⁰. Complexes (III) and (IV) contain more nitrogen (1 and 0.5 atoms per formula unit respectively) than required for $\text{Mo} : \text{N}_2\text{H}_4 = 2 : 1$. This extra nitrogen is not oxidized by iodate and is partially released as ammonia by hydrolysis of compound (III) (Fig. 1). There is no evidence for coordinated dinitrogen in these complexes; there is, for example, no infrared band at $1,700\text{--}2,200\text{ cm}^{-1}$ (refs. 11 and 12). The presence of bridging imide (NH^{2-}) groups is consistent with our data but the presence of water and hydrazine prevents direct proof of the presence of imide groups.

Because hydrazine is a reducing agent we could not determine molybdenum oxidation states in compounds (III)–(V) directly by oxidimetric titration. In separate experiments iodate quantitatively oxidized low-valent molybdenum to molybdenum (V) and hydrazine to nitrogen. The iodate titrations determined the total reducing equivalents of our compounds. Between the molybdenum(V) compound (II) and its product of reaction with hydrazine in the cold, compound (V), there was a difference of four reducing equivalents, equivalent to one molecule of hydrazine per two molybdenum(V). Thus compound (V) is formed by coordination of hydrazine without change of molybdenum oxidation state in agreement with the stoichiometry ($\text{Mo} : \text{N} = 1 : 1$). Compound (IV) obtained together with ammonia by heating compounds (II) and (V) with hydrazine hydrate and water and by prolonged reaction of compound (III) with cold water had two more reducing equivalents than compound (V) indicating for compound (IV) a molybdenum oxidation state of +4 and $\text{Mo(IV)} : \text{N}_2\text{H}_4 = 2 : 1$. Compound (III) is hydrolysed to compound (IV) with loss of ammonia but without change in reducing equivalents and so also has $\text{Mo(IV)} : \text{N}_2\text{H}_4 = 2 : 1$ with extra nitrogen—bridging imide—not oxidized by iodate (see above).

Reaction of the binuclear molybdenum(III) complex, (I), with hydrazine hydrate involves (a) coordination of hydrazine as a bridging ligand between two molybdenum atoms, (b) oxidation of molybdenum(III) giving a complex of molybdenum (IV) with bridging hydrazine and imide groups formed through reduction of hydrazine. Reaction of the binuclear molybdenum(V) complex, (II), under mild conditions with hydrazine hydrate involves only coordination of hydrazine also as a bridging ligand giving a molybdenum(V) complex, (V). Complex (V) may be reduced by hydrazine to a molybdenum(IV) complex, (IV), containing bridging hydrazine and imide groups. Reduction of molybdenum(V) by hydrazine is similar to the reduction of molybdenum(VI) (which gives dinitrogen and ammonia)^{13,14}. Coordinated imide groups may undergo hydrolysis but coordinated hydrazine apparently does not react with water. Thus in our system binuclear molybdenum(III) provides two electrons for the reduction of hydrazine, and is oxidized to a molybdenum(IV) complex which contains imide groups and from which ammonia is released on hydrolysis. This reaction is similar to the last stage

of a proposed nitrogen fixation mechanism which involves formation of ammonia from amide groups coordinate to molybdenum^{1,2} and our work, therefore demonstrates the feasibility of such a reaction at molybdenum.

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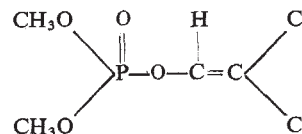
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Mutagenicity of Dichlorvos

THERE have been several conflicting reports on the genetic effects of Dichlorvos (2,2-dichlorovinyl dimethyl phosphate),



which is the active ingredient of Shell's pesticide, 'Vapona'. Dichlorvos is present in 'Herkol', 'Dedevap', 'Oko', and 'Mafu' which are listed as synonyms by Epstein and Legator¹. Sax and Sax² reported chromosome aberrations in onion root tips. Löfroth³ working with pure Dichlorvos demonstrated, *in vitro*, the alkylation of calf thymus DNA in which N-7-methylguanine was the major product with a yield of 1% after 60 h treatment. According to Epstein and Legator¹ who cite the work of Michalek and Brockman⁴ Dichlorvos is mutagenic in *Neurospora*. However, this is a mistake, as Michalek and Brockman using the Adenine 3 region of *Neurospora crassa* were unable to demonstrate any mutagenic effect of Dichlorvos.

Lederberg⁵ has stated that "Experimental evidence of mutagenic capability should be a danger signal that a compound may also be capable of other, somatic hazards through its action on DNA and other cellular constituents". We report here that Dichlorvos is mutagenic to bacteria. We have screened a number of pesticides and other biocides for possible mutagen activity (Table 1) and only Dichlorvos and Captan (N-trichloromethylthio-4-cyclohexene-1,2-dicarboximide, which is also known as Orthocide) have been shown to be mutagenic. The mutagenicity of Captan has been reported previously^{6,7}. We used an auxotrophic mutant of *Escherichia coli* (WP 2 Try⁻) which can mutate to prototrophy either by true reverse mutations at the tryptophan locus or by the induction of ochre (UAA) suppressors⁸. No attempt was made to distinguish between these two types of back mutation. Cells were grown overnight at 37° C in glucose-salts medium supplemented with $10\text{ }\mu\text{g ml}^{-1}$ of L-tryptophan and plated on agar plates containing glucose and mineral salts plus $1\text{ }\mu\text{g ml}^{-1}$ of L-tryptophan. Approximately 2×10^8 cells were added per plate and mutants

(revertants to tryptophan independence) were scored after incubation at 37° C for 48 h. Tests for mutagenicity were made by cutting 'Vapona' into small strips (approximately 20 mm²) and placing these strips on the surface of the seeded agar lawn. This system has recently been used by Clarke⁶ in his studies on the mutagenicity of Captan. In many instances, especially when using a newly opened strip of 'Vapona', a large zone of growth inhibition surrounded the strip. Induced mutants

Table 1 Pesticides and Biocides Non-Mutagenic in Bacteria (Reversion of *E. coli* WP2 TRY- to Prototrophy)

Common name and synonyms	Chemical name and composition	Manufacturer
<i>Aldrin</i> <i>Drinox</i> <i>Seedrin</i>	1, 2, 3, 4, 10, 10-hexachloro-1, 4, 4a, 5, 8, 8a-hexahydro-1, 4-endo-exo-5-8-dimethanonaphthalene	Shell
<i>Carbaryl</i> <i>Sevin</i>	1-naphthyl N-methyl-Carbamate	Carbide
<i>Chlordane</i> <i>Chlor Kil</i> <i>Corodane</i> <i>OrthoKlor</i> <i>Synklor</i>	Mixture of 60% 1, 2, 3, 4, 5, 6, 7, 8-octa-chloro-3a, 4, 7, 7, 7a-tetrahydro-4, 7-methanoindane and 40% related compounds	Vesicol
<i>DDT</i> <i>Genitox</i> <i>Anofex</i> <i>Chlorophenothane</i> <i>Dichloro-</i> <i>Diphenyltrichloro-</i> <i>ethane</i>	1, 1, 1, trichlor-2, 2-bis (p-chlorophenyl) ethane	Lebanon Allied Diamond Montrose Olin Geigy
<i>Diazinon</i> <i>Alfa-Tox</i> <i>Sarolex</i> <i>Basudin</i> <i>Spectracide</i> <i>Ag. 500</i>	0, 0-diethyl 0-(2-iso-propyl-4-methyl-6-pyrimidinyl) phosphothioate	Geigy
<i>Dicofol</i> <i>Kelthane</i>	1, 1-bis (p-chlorophenyl) 2, 2, 2-trichloroethanol	Rohm and Haas
<i>Dieldrin</i> <i>Octalox</i> <i>Panoram D-31</i>	Not less than 85% of 1, 2, 3, 4, 10, 10-hexachloro-6, 7-epoxy-1, 4, 4a, 5, 6, 7, 8, 8a-octahydro-1, 4-endo-exo-5, 8-dimethanonaphthalene	Shell
<i>Dimethoate</i> <i>Cygon</i> <i>Rogor</i>	0, 0-dimethyl S-(N-methyl-carbamoylmethyl) phosphorodithioate	Cyanamid
<i>Karathane</i> <i>Dinocap</i> <i>Arathane</i> <i>Mildex</i>	2-(1-methylheptyl)-4, 6-dinitrophenyl crotonate	Rohm and Haas
<i>Lindane</i> <i>Gamma BHC</i>	1, 2, 3, 4, 5, 6-hexachloro cyclohexane. At least 99% gamma isomer	Diamond Hooker
<i>Malathion</i> <i>Cythion</i> <i>Malaspray</i> <i>Chemathion</i>	0, 0-dimethyl phosphorodithioate of diethylmercaptosuccinate	Cyanamid Chemical Industries
<i>Methoxychlor</i> <i>Marlate</i> <i>DMDT</i> <i>Methoxy DDT</i>	2, 2-bis (p-methoxyphenyl)-1, 1, 1-trichloroethane	DuPont Chemical Formulation
<i>Piperonyl Butoxide</i> <i>Butacide</i>	Butyl carbityl-6-propyl-piperonyl ether (80%) and related compounds (20%)	F.M.C.
<i>Pyrethrins</i> <i>Pyrethrum</i>	Numerous	Chemical Industries F.M.C. Penick Prentiss M.G.K.
<i>Rotenone</i> <i>Protex</i>	Rotenone	Chemical Industries F.M.C. Penick Prentiss

All compounds were tested at a concentration of 10% (active ingredient) dissolved or suspended in phosphate buffer (pH 7.0; 0.07 M). The quantity of test substance per disk was approximately 1 mg. Formulae and synonyms from Epstein and Legator¹.

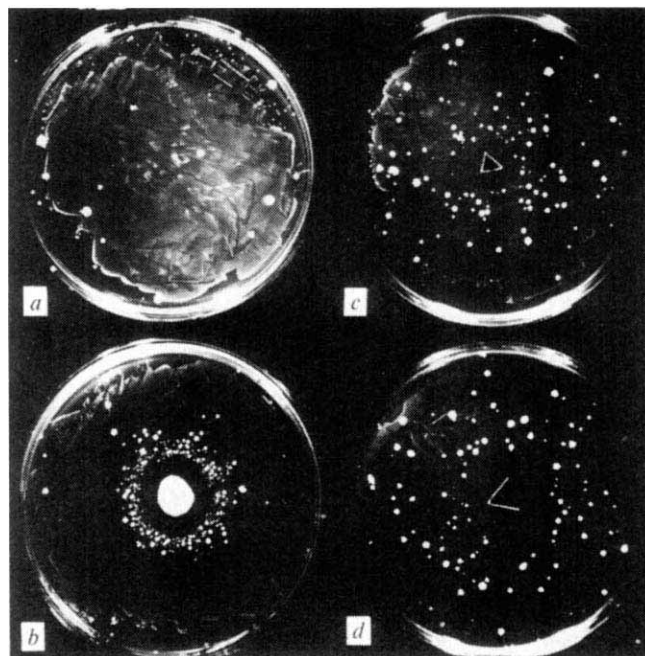


Fig. 1 Agar plate assay for mutagens. *E. coli* WP2, Try⁻ were plated at 2×10^8 cells per plate. Plates contained mineral salts and glucose supplemented with 1 µg per ml. of L-tryptophan. Mutant colonies counted only within the obvious veil or lawn. Colonies show up as white spots. *a*, Control. *b*, Nitrosomethylguanidine (10 µg on central disk). Note zone of no bacterial growth and large number of mutants. *c* and *d*, With 'Vapona' strip. Note zone of no bacterial growth and increased mutant yield.

usually appeared in a ring around the strip and beyond the inhibition zone. When N-methyl-N'-nitro-N-nitrosoguanidine was used as a test mutagen the inhibition zone was large and the number of mutants too large to count with any accuracy. The test system is illustrated in Fig. 1.

Table 2 Reversion of *E. coli* WP2 TRY- to Prototrophy when Exposed to Dichlorvos

Experiment	Treatment	Number of plate mutants per 10^8 cells ($\pm$ S.D.)
Experiment 1	Control	5.6 $\pm$ 0.6
	Dichlorvos	16.0 $\pm$ 5.1 *
Experiment 2	Control	6.3 $\pm$ 2.1
	Dichlorvos	17.4 $\pm$ 1.9 *
Experiment 3	Control	7.0 $\pm$ 3.1
	Dichlorvos	46.1 $\pm$ 12.4 *
	Control N-methyl-N'-nitro-N-nitrosoguanidine	7.0 $\pm$ 3.1 > 300 *

*No correction for lethality. Plates in quadruplicate in all experiments.

Results, which are expressed in terms of the number of mutants per 1×10^8 plated cells, are shown in Table 2, and it is clear that Dichlorvos increases the mutant yield by a factor of about 3; in a third experiment a factor of about 6 was noted. These values are underestimates as no attempt to correct for the varying kill was made (not easy with this screening system). The volatility of Dichlorvos, exposure temperature and the ability of bacterial repair systems to modify this genetic damage remain to be investigated. Our results indicate clearly the mutagenic action of this widely used and much discussed pesticide⁹.

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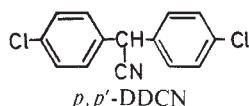
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Formation of bis(*p*-Chlorophenyl)-acetonitrile (*p,p'*-DDCN) from *p,p'*-DDT in Anaerobic Sewage Sludge

WE report the formation of bis(*p*-chlorophenyl)acetonitrile, (*p,p'*-DDCN) together with 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p'*-TDE) and other products from 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p'*-DDT) in the presence of biologically-active anaerobic sewage sludge.



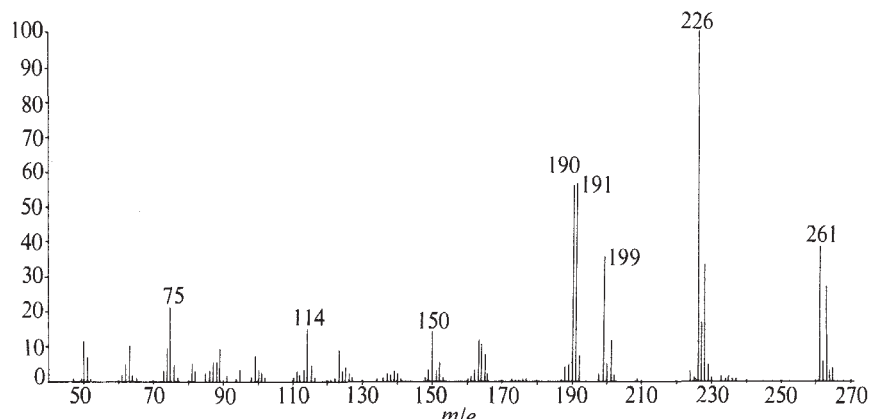
Fries¹ observed that, in spite of extensive investigation of the anaerobic degradation of DDT, little has been firmly established except that TDE is a major degradation product. In the present study, the identification of *p,p'*-DDCN, as an important nitrogen-containing environmental breakdown product of *p,p'*-DDT, was facilitated by the use of combined gas chromatography-mass spectrometry in conjunction with radiochemical techniques. The incorporation of radiolabelled DDT made it possible to detect the diverse DDT-derived products formed in the complex sewage environment. Our results were obtained within the context of a wider investigation of the fate of DDT and other organochlorine pesticides in estuarine sediments and also in sewage sludge.^{2,3} Hill and McCarthy⁴ have noted the very rapid transformation of DDT to TDE in anaerobic sewage sludge and Halvorson *et al.*⁵ have advocated the use of sewage bacteria to provide a rapid biodegradability criterion for insecticides.

Anaerobic sewage sludge (400 ml., 5% w/w solids, pH 8.2) from the 35° C anaerobic digester, Avonmouth Foul Water Treatment Works, Bristol, was incubated for 88 days at 37° C in a vessel fitted with a fermentation lock, during which a total of 7.45 mg ¹⁴C-*p,p'*-DDT (4.7 μCi) and 20 g minced beef were

added, the latter to enhance microbiological activity. ¹⁴C-*p,p'*-DDT (phenyl ring-¹⁴C(u), 67 μCi/mg) supplied by the Radiochemical Centre, Amersham, Bucks, and unlabelled *p,p'*-DDT (99+ % pure, Aldrich Chemical Company) were used, purity being verified by gas liquid chromatography (GLC) and thin layer chromatography (TLC). Addition of *p,p'*-DDT in ethanol (200 μl. aliquots) was as follows: 2.82 mg (0 μCi) on day 0; 0.03 mg (2.35 μCi) on day 5; 4.60 mg (2.35 μCi) on day 42. Minced beef (20 g) was added on day 26. When the incubation terminated, the sludge was centrifuged and the aqueous layer filtered and counted. The filtrate contained 0.4 μCi. The solid residue was extracted rapidly three times in the cold with isopropanol : heptane (4 : 1) using a modified procedure of Dole and Meinertz⁶ and a total of 1.5 μCi (32% total label) was recovered. The residual solid was counted (Nuclear Enterprises NE 221 gel scintillator) and was found to retain a further 1.5 μCi activity. The Dole-Meinertz extract was first examined by GLC ('Perkin-Elmer F11' gas chromatograph with ⁶³Ni electron capture detector (ECD) using on-column injection and 6 foot × 0.25 inch silanized glass column of 1.5% OV-17, 1.95% QF-1 mixed phase on Diatoport S, 80-100 mesh; column temperature 200° C isothermal). Comparison with standards (Analabs, Inc.) revealed only trace quantities (<1% GLC peak area of total extract) of *p,p'*-DDT while the *p,p'*-TDE peak (retention time relative to *p,p'*-DDT, 0.84) predominated. Other GLC peaks were noted at retention times relative to *p,p'*-DDT of 0.37, 0.57, and 0.62. Enriched anaerobic sewage incubated for the same length of time and extracted in an exactly similar fashion, but without the addition of *p,p'*-DDT, showed none of the above ECD sensitive peaks in the extract.

Thin layer chromatography (Kieselgel G with *n*-hexane; ethyl acetate; acetic acid, 15 : 1 : 0.01) of the extract, followed by radioscanning of the TLC plates, revealed three zones of activity; zone A (*R_F* 0.3 to 0.6) including *p,p'*-DDT and *p,p'*-TDE, zone B (*R_F* 0.1 to 0.3) and zone C (*R_F* 0.0 to 0.1) in the ratio 62 : 29 : 9. TLC zone B was found to give only one major peak on further ECD-GLC analysis (retention time relative to *p,p'*-DDT, 0.62). Although flame ion detector GLC analysis of zone B extract using a 'Pye 104' gas chromatograph also fitted with a 'Panax' gas flow proportional counter revealed the presence of many other components in this extract to which the ECD detector did not respond, radioactivity was confined solely to the major ECD-sensitive peak. Combined gas-chromatography-mass spectrometry (GC-MS) of the zone B material yielded the mass spectrum shown in Fig. 1. High resolution probe mass spectrometry ('AEI MS 902') of this material gave exact masses for the ions at *m/e* 261 and 226 of 261.0094 (*C*₁₄*H*₉*NCl*₂⁺ requires 261.0112) and 226.0424 (*C*₁₄*H*₉*NCl*⁺ requires 226.0424), respectively. The intensities of the chlorine isotope peaks in the low resolution mass spectrum were in accord with these compositions. The observed molecular formula of *C*₁₄*H*₉*NCl*₂ seemed best accommodated as *p,p'*-DDCN and accordingly a sample of *p,p'*-DDCN was synthesized by the method of Skerrett and Woodcock⁷. This material, m.p. 90-90.5° C (lit.⁷ 88-89° C), exhibited identical GLC

Fig. 1 Mass spectrum of *p,p'*-DDCN produced in anaerobic sewage sludge recorded using a 'Varian MAT CH-7' low resolution mass spectrometer (Watson-Biemann separator) in conjunction with a 'Varian Aerograph 1200' chromatograph fitted with a silanized stainless steel column, 8 foot × 1 mm (i.d.) of 1.5% OV-17, 1.95% QF-1 mixed phase on 'Diatoport S', 80-100 mesh at 210°. Helium carrier gas, electron energy, 70 eV; accelerating voltage, 3 kV. The spectrum was obtained by scanning over a mass range of 10-600 (1 s/decade). The retention time of the peak scanned was 6.7 min and corresponded approximately to 20 ng material.



retention time by coinjection on a column of OV-17/QF-1 mixed phase with the zone B ECD-sensitive major GLC peak. It had also a TLC R_F value of 0.15 relative to that of p,p' -DDT of 0.48 on the same TLC plate in the conditions described above. The mass spectrum (GC-MS) of the synthetic material was identical with that shown in Fig. 1, finally confirming zone B material as p,p' -DDCN.

GLC quantitation of the Dole-Meinertz extract from the DDT sewage incubation revealed a mass ratio of p,p' -TDE to p,p' -DDCN of 0.42 to 1.00 (ECD-GLC peak area ratio 1:0.22), corresponding to a p,p' -DDCN yield of 11.7%, based on p,p' -DDT incorporated. Similar degradation of p,p' -DDT was also observed in preliminary experiments in which ^{14}C - p,p' -DDT was incubated at 35°C under hydrogen in unenriched anaerobic sewage sludge for periods from one to four weeks.

We are, however, unable to decide at present whether this material is produced microbiologically or chemically in the nitrogen-rich alkaline environment of anaerobic sewage sludge. Possible routes include via p,p' -DDA→amide→nitrile or more directly from p,p' -DDT. p,p' -DDCN may also be produced in other anaerobic environments possessing similar properties (certain estuarine sediments). Future survey work on pesticide residues in the environment should not ignore the contribution of the more polar degradation products. The importance of these compounds is liable to be underestimated in those cases, where, as with p,p' -DDCN, the ECD detector is relatively insensitive. Reactions revealed by such studies, for example the conversion of $-\text{CCl}_3$ to $-\text{CN}$, should be of general significance in pollution studies. We do not know of studies on the toxicological and related properties of p,p' -DDCN in the environment.

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Bis-(*p*-Chlorophenyl)-Acetonitrile (DDN), a New DDT Derivative formed in Anaerobic Digested Sewage Sludge and Lake Sediment

To investigate the degradation process of DDT (2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane) in a system in strong putrefaction, one litre of activated sludge was fed with 100 mg of p,p' -DDT, fortified with ^{14}C -DDT (5 μCi), and containing DDD (2,2-bis-(*p*-chlorophenyl)-1,1,1-dichloroethane, 4.0%) and DDE (2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethylene, 3.1%) as contaminants.

The sludge was incubated for 8 days at 20°C in an atmosphere of nitrogen with a magnetic stirrer. To determine the half life

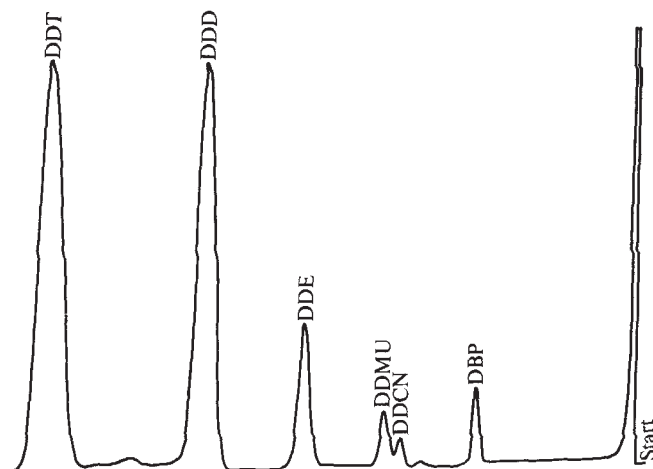


Fig. 1 Gas chromatogram of extract from anaerobic digestion of sludge from a sewage treatment plant, to which was added 100 p.p.m. of DDT. Sample taken 7 h after start. GC column, 4% 'SF 96'. Temperature, 182°C.

of DDT small portions of the sludge were removed at 0, 3, 5, 7, 16, 88 h and 8 days after start of the incubation and analysed by gas chromatography. 1 ml. samples were mixed with methanol (1 ml.) and shaken with hexane (15 ml.) for 1 h. After proper dilution the hexane solution was injected into a 'Varian 1400' gas chromatograph fitted with an electron-capture detector. The 160 cm all-glass column (internal diameter 0.18 cm) was filled with 4% 'SF 96' methyl silicone oil on 100–120 mesh silanized 'Chromosorb W'. The oven temperature was chosen to give a retention time of 20 min for DDT with a nitrogen gas flow of 25 ml. min⁻¹ (~180°C).

The DDT was rapidly consumed, with a half life of only 7 h (Fig. 1), partly under transformation to DDD, DBP (p,p' -dichlorodi-phenylbenzophenone), DDMU (1-chloro-2,2-bis-(*p*-chlorophenyl)-ethylene) and the new transformation product (peak 2 in the chromatogram shown in Fig. 2, now identified as DDCN). The original low content of DDE disappeared within 48 h (Fig. 3).

To isolate the new transformation product the sludge was centrifuged at 25,000 r.p.m., with complete sedimentation of the sludge and no ^{14}C activity in the water phase. The centrifugate was air dried (22.5 g) on filter paper and ground

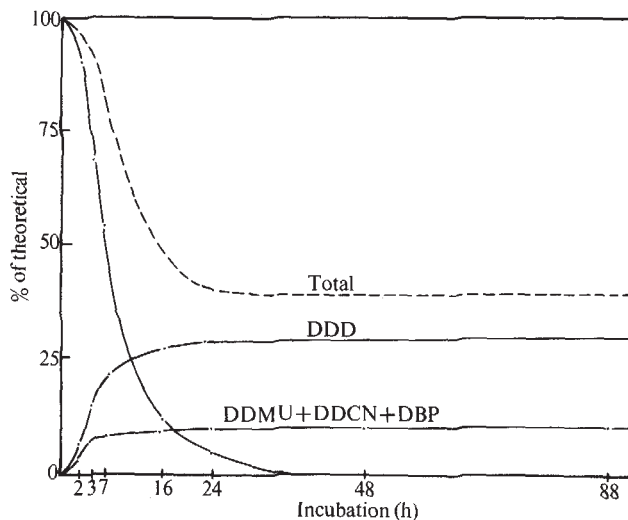


Fig. 2 Rate of DDT decrease following anaerobic digestion of sludge from a sewage treatment plant to which DDT was added. The figure also shows the rate of formation of DDD and three "minor metabolites" (DDCN, DDMU and DBP) as well as the total molecular recovery of DDT in the form of "metabolites" possible to determine by means of gas chromatography.

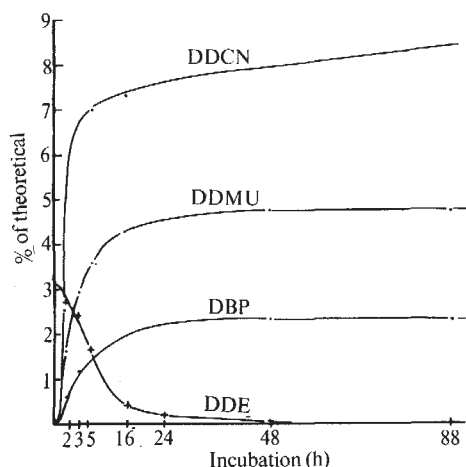


Fig. 3 Rate of DDE decrease in anaerobic digestion sludge from a sewage treatment plant, as well as the formation of DDCN, DDMU and DBP. Initial DDT concentration 100 p.p.m.

before Soxhlet extraction with a 1:1 mixture of acetone and hexane. The ^{14}C -activity recovered was 2.5 μCi (50%), in agreement with the previously observed extent of transformation to products detectable by this method (Fig. 2).

The concentrated extract was separated on a partly deactivated aluminium oxide column (70 g, 5% water). Elution with hexane (460 ml.) gave almost pure DDD as shown by gas chromatography (GC), with ^{14}C activity responsible for 24% of the activity fed to the sludge. On elution with ethyl ether in hexane (10%, 250 ml.) a fraction was obtained, containing the new DDT transformation product (9% of the initial ^{14}C activity), contaminated with traces of DDT, DDD, DDMU and DBP. A final elution with ethanol (400 ml.) gave a fraction of unidentified products, adding up the recovery of ^{14}C activity to 40%. Before mass spectrometer analysis the DDN was further purified by preparative thin layer chromatography, using 1 mm silicagel HF 254 (20 $\times$ 20 cm) and ethyl ether in hexane (20%) as eluant. The chromatogram was covered with a 'Kodak' X-ray film for three days and after development the R_f value of DDCN was determined by exclusion of spots corresponding to known DDT metabolites such as DDA (R_f 0.0), DBP (R_f 0.39), DDD (R_f 0.48), DDMU (R_f 0.64) and DDT (R_f 0.84) and verified by GC.

An extract of the zone containing DDCN (R_f 0.28) was analysed on an LKB 9000 combined gas chromatograph-mass spectrometer, using the column system described above.

The mass spectrum with molecular ion at m/e 261 (isotopic pattern m/e 261:263:265 with relative intensities 1.0:0.62:0.10), abundant ion at m/e 226 (m/e 226:228 with rel. int. 1.0:0.33), m/e 191 and m/e 190 as the most abundant ions, were essentially identical with a mass spectrum obtained from an authentic sample of bis-(*p*-chlorophenyl)-acetonitrile (DDCN) synthesized according to Grummit and Marsh¹ (m.p. 90–91° C, IR and NMR spectra as expected).

This identification was confirmed on the chromatographic system described. The tendency of DDCN to undergo autoxidation forming DBP in ethanolic potassium hydroxide, analogous to diphenylacetonitrile², was shown to be suitable for confirmation of DDCN at low concentrations. A solution of DDCN in hexane was mixed with an equal volume of potassium hydroxide solution (1 M) in ethanol (96%) and shaken for 1 h. After adding five times the volume of water the DBP was indicated on GC in the hexane phase.

At low concentrations (less than 0.5 p.p.m.) the DDCN (being a weak base) could also be extracted from a hexane solution by shaking with an equal volume of concentrated sulphuric acid for 5 min. By careful dilution of the sulphuric acid with 1/4 of volume of water under cooling in a dry ice-acetone mixture and subsequent shaking, the DCN was almost quantitatively extracted back to the hexane phase.

The concentrations of DDD and the DDCN in the digestion experiment did not show any significant change after the complete consumption of DDT (Fig. 3), excluding further metabolization and indicating a direct formation of DDCN from DDT. No DDCN could be detected after feeding DDD and DDE to sludge in similar experiments. It could not be determined whether DDCN was formed via a metabolic pathway, or originated from a direct reaction with substances present in the sludge. A reaction path similar in some respects to the formation of benzonitrile from α -trichlorotoluene and ammonium chloride at elevated temperature³ did not seem improbable and slow formation of DDCN was indicated when a 1:1 mixture of DDT and ammonium chloride was heated to 150° C in a closed tube.

DDCN was even found present in a natural system. A sample from the sediment layer of the Lake Mälaren in Sweden contained DDCN in 0.6 p.p.m./dry weight. About 5 ml. of the sediment (corresponding to 1.5 g dry material) was centrifuged and the water discarded. To the sediment was added 5 ml. of a 4:1 mixture of acetonitrile and formic acid and then 2 ml. of hexane. The mixture was shaken for 2 h, and then for a further 5 min after the addition of 7 ml. of water, a procedure yielding 100% partition of the DDCN to the hexane phase. The hexane phase was further purified by means of partition chromatography, using a column (0.5 $\times$ 5 cm) of dimethyl formamide (0.5 g) on silicagel (0.5 g), prewashed with hexane (25 ml.). The hexane solution (1 ml.) was added to the column and eluted with hexane, collected in 4 ml. fractions. Any DDCN present comes in the third fraction together with traces of DBP. Analysis on two GC systems (the SF 96 coating and the commonly used DC 200/QF 1 mixture) gave the above result and the identity of the DDCN was also confirmed by the potassium hydroxide and sulphuric acid methods described above. The recovery of DDCN added to sediment at the 0.07 p.p.m. level was above 90%. By the same method a sample of digested sludge from the sewage water treatment plant of Uppsala was shown to contain 0.012 p.p.m. of DDCN on dry weight basis.

DDCN has not previously been found in nature, probably due to its polar properties, which complicate separation from common substances, its low chemical stability and relatively low response to the almost indispensable electron capture detector (about one fourth of DDDs) as well as its tendency to form DBP on treatment with bases, a reaction typical of the dicofol-like substances also formed from DDT in different biological systems⁴.

At present little is known about its action against different organisms or tendency to accumulate in higher organisms but it is worth noting that the non-chlorinated analogue has been used as a herbicide and that DDCN is patented for use against several organisms in soil⁵.

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BOOK REVIEWS

Structure of Knowledge

Organization of Memory. Edited by E. Tulving and W. Donaldson. Pp. xiii+423. (Academic: New York and London, April 1972.) \$17.50.

It is, of course, the organization of our knowledge that makes possible the use of that knowledge in mental processes and behaviour. The fact that information is stored is clearly a prerequisite, but if memory were simply retention, and knowledge were simply stored like so much furniture in a warehouse, it would be useless. Evidently information is organized to reflect its semantic significance, and it is this that makes such human activities as thought and language possible. This book is fascinating because much of the material in it is related to this issue which might be thought of as one of the most important in psychology at present.

Because there are some aspects of memory which are measurable, many experimental psychologists have chosen to start with these. Thus success in recalling lists of words can give clues as to how the remembered material is organized by a subject both at the time of learning and in memory. The greater part of the book is devoted to chapters of varying quality in which experiments of this general kind and the conclusions arising from them are discussed. Perhaps the best of these chapters is by Bower, who with several associates has made quite successful attempts to unravel the structure of semantic meaning with which subjects invest even meaningless material in order to attempt to remember it. But the tasks presented to the subjects in paired associate learning experiments, or even in free recall tests of lists of words, are not necessarily revealing applications of our mental apparatus. One might indeed wonder why, if memory is so important for human intelligence, human performance on memory tasks is so feeble. There would certainly be nothing remarkable about a computer or for that matter a man armed with a pencil and paper able to store and regurgitate a handful of words. But this comes back again to the fact that

it is not retention as such that is important but organization. If in the more traditional research on memory, retention was seen as important, it was perhaps because treating memory as some kind of receptacle for input information was a theoretical device which could be handled, while models for organization just did not exist.

But this has now changed, and in this volume the most striking chapters attack the organizational issue directly. Rather than asking how people perform when faced with trivial memory tasks that they are not quite able to accomplish, the authors of these chapters are mainly concerned with how knowledge is organized to make possible the understanding of natural language. In such matters our use of computers is central. But this use does not emphasize the triviality of the task; rather by setting out to write computer programs which will understand natural language, we can begin to appreciate what some of the central psychological issues of human memory really are.

Collins and Quillian in their chapter emphasize this point even in their title, "How to make a language user". Quillian was one of the first to program a network of nodes and directed links representing a structure of semantically organized verbal knowledge. In his system nodes represented words or concepts and links of specific kinds represented certain attributes and relationships of these concepts. The system contained dictionary definitions, coded into the format of nodes and links. On being asked to relate two words the computer traversed this semantic network and output sentences in pidgin English which compared and contrasted the input words in a way which seemed intuitively reasonable to human language users. Subsequently Quillian developed his program to show how his network could interpret segments of English, coping with anaphoric reference by making certain deductions from the structure of stored information. Collins and Quillian have also conducted a series of psychological experiments to investigate how human language users organize information

about attributes and relations of words they use. In their present paper they discuss computational and experimental work, pointing to problems such as the deployment of tacit knowledge in many cognitive tasks and the uses of analogy and metaphor which with the newer computational methods seem at least to be in sight, if not quite within reach.

Since Quillian's first papers were published, Fillmore's account of case grammar has appeared. In this account verbs are represented as relationships taking certain actual or potential arguments such as actor, instrument, location, etc. Kinch's chapter contains an interesting discussion of the properties of case grammars and related forms, in the context of how lexical information is organized in memory. In another interesting chapter, Rumelhart, Lindsay and Norman also capitalize on this development in linguistics, as well as on the type of program recently written by Winograd, in which knowledge is represented as a set of procedures which can call each other. Rumelhart *et al.* describe a formal notation to represent concepts (with their relationships and attributes), events and sequences of events, and they also describe an equivalent computational form. A curious aspect of their account is the rather sinister thread of violence running through almost all the examples used: "Hearing the snarling and growling, Perrault raises his rifle", "John murders Mary at Luigi's", even "John breaks a window of his house with a hammer because he wants to collect the insurance" and so on and so on. Whether the preference for words like "hit" and "break" in linguistic analysis reflects in more than one sense some primitive significance of such concepts is not clear. Although Rumelhart *et al.* seem only to have programmed a small part of their model, and indeed have only used that to explain learning of lists, what is clear is that some form of model exhibiting and depending upon the semantic structure of knowledge is going to be central to any understanding not only of memory, but of language, thought, perception, and indeed all mental processes.

KEITH OATLEY

Mercury Pollution

Environmental Mercury Contamination. Edited by Rolf Hartung and Bertram D. Dinman. Pp. ix+349. (John Wiley: New York and London, September 1972.) £9.40.

THERE is increasing public awareness of the role of mercury in our environment. It is appropriate, therefore, that two leading health scientists, Dr Hartung and Dr Dinman, should undertake the task of editing a volume based on an International Conference on Environmental Mercury Contamination held in Ann Arbor, Michigan, in 1970. The result is an outstanding compilation and assessment of our present state of knowledge on mercury, an indication by the editors of what is still needed to be done, and an unemotional approach to the difficult question of mercury environmental threshold limit values. The data presented dispel immediate fear of dangerous mercury contamination in North America without permitting complacency.

The papers presented cover four main fields: the occurrence of mercury in the environment and in man, methods of mercury analysis, environmental dynamics of mercury and the biological effects of mercury compounds. Thus there is valuable information both for public health authorities and for research workers on the sources and subsequent distribution of mercury, the role of methylation processes and food chain phenomena, the effects of acute and chronic exposures of man and wildlife to both organic and inorganic mercury compounds, and from the chemist's standpoint, an assessment of present analytical methods. Bibliographies are provided with each paper and excellent summaries, comments and discussion papers have been supplied by the editors. It is to be regretted that some of the figures illustrating mercury geographical distributions are unreadable.

A large proportion of the work reported is concerned with mercury contamination in North America but there is a lesson to be learnt by all countries not yet concerned with pollution. The Japanese suffered the consequences of uncontrolled industrial mercury discharge and the subsequent Minamata and Niigata disasters are well documented in this book. Sweden quickly grasped the implications of high mercury fish values in food chains before severe biological effects developed in humans. Now the North American environment, particularly around the Great Lakes, has been studied in depth with the results reported at this conference. One of the principal difficulties facing all workers in this field concerns the environmental dynamics of mercury which are greatly complicated by the existence of several compounds of

mercury, all of which have different biological properties. Furthermore, inter-conversions between compounds can occur, the most important of these being methylation of mercury in natural systems. This book will prove to be a most useful reference volume. It provides a wealth of information for all interested in trace elements in general and heavy metals in particular and their impact upon society and the environment.

WILLIAM TAYLOR

The New Primatology

The Functional and Evolutionary Biology of the Primates. Edited by Russell Tuttle. Pp. xxii+487. (Aldine Atherton: Chicago and New York, April 1972.) \$15.

THIS volume of collected papers on various aspects of primatology provides further evidence of the tremendous importance of the Burg Wartenstein Symposia of the Wenner-Gren Foundation. These regular meetings of selected groups of specialists provide an excellent basis for the discussion and clarification of specific areas of research in physical anthropology, and the published papers are of immediate interest to many workers in the field. This particular volume covers a fairly large field, bringing in studies of fossil primates, cranial morphology, the central nervous system, post-cranial morphology and primate behaviour. Among the nineteen papers, there are several real gems—such as the succinct review of hominoid fossils (Simons and Pilbeam), the detailed survey of South African hominid material (Tobias), an extremely perceptive discussion of the "arboreal theory" of primate evolution (Cartmill), an explicit summary of long-term comparative studies of primate brains (Stephan), and an immaculate anatomical study of the morphology of the hominoid wrist (Lewis). There are also several theoretical papers analysing the scope for mathematical techniques (Oxnard; Cohen) and the application of special research techniques to the study of primate functional morphology (for example, Basmajian's paper on electromyography). Individually, many of these papers will prove to be indispensable for primatologists in various fields. The only criticism that might be made is that the range of the papers is too great, and that the aims of the Burg Wartenstein Symposia might have been more aptly met by concentration on just one of the several themes covered. The most obvious flaw in this respect is the inclusion of three papers on the behaviour of cercopithecoid monkeys,

which bear little relationship to the other papers in the book although they are of interest in their own right. If the Wenner-Gren Symposia are to maintain their customary exceptionally high standard, it is essential that each Symposium should concentrate on a particular area of research, as was the case (for example) with old world monkeys.

One of the drawbacks with symposia which cover too wide a field is the automatic imbalance which emerges in the published papers. A very good example of this is provided by the dismissal of the "vertical-clinging-and-leaping concept" in the papers written by Szalay and Cartmill. Both authors have completely misinterpreted the original subject-matter in the same way, maintaining that Napier and Walker postulated vertical-clinging and leaping as the ancestral primate pattern of locomotion. What Napier and Walker in fact said was that vertical-clinging and leaping should possibly be regarded "as the earliest locomotor specialization of primates". In view of the fact that this volume is intended as a discussion of primate functional biology, it is a pity that a concept as important as this should not have been adequately discussed. Szalay and Cartmill have—so to speak—eaten the embryo along with the extra-embryonic membranes.

There is also some degree of imbalance in the discussion of the evolution of the primate nervous system. Despite his generally meticulous approach, Stephan really does seem to believe that the "basal insectivores" exhibit brains relatively identical in size and gross structure to those of Cretaceous ancestral mammals, and that various primates have been arrested at different stages in the evolutionary elaboration of the brain: "The graph based on the indices of neo-cortical progression shows that within the Primates many different evolutionary stages are preserved in extant species." Although this over-simplification is to some extent offset by Radinsky's neat account of primate endocasts (which actually illustrate gross brain structure at various points in the fossil record), even Radinsky accepts the widespread (but unproven) notion that there has been a reduction of olfactory areas throughout primate evolution. It is true that primates generally have relatively smaller olfactory areas than extant "basal insectivores"; but it has yet to be shown that any extant primate species has absolutely smaller olfactory areas than would have been found in an actual Cretaceous mammal of the same body size. It is only in terms of the latter comparison that "reduction of the palaeocortex and bulbus olfactorius" can have any real meaning. Again, this topic deserves adequate treatment.

Although one can criticize the fact that the papers do not cover a well-defined subject in sufficient detail, this is nonetheless a valuable book for the primatologist's bookshelf. The wide range covered can perhaps be excused with the observation that several of the papers share the common theme of a search for new techniques in the study of primate biology. Overall, one is left with the impression that a stage has now been reached where the study of primates will expand in a number of new directions simultaneously. If this is the case, *The Functional and Evolutionary Biology of the Primates* will probably become a standard reference work.

R. D. MARTIN

¹ Napier, J. R., and Walker, A. C., *Fol. Primat.*, 6, 204 (1967).

Water, Water

Water: a Comprehensive Treatise. Edited by Felix Franks. Volume 1. *The Physics and Physical Chemistry of Water.* Pp. xx+596. (Plenum: New York and London, 1972.) \$43.00. Special Subscription Price \$32.50 per volume.

THE importance of water in all aspects of terrestrial life is universally recognized, but, even so, the promise of a four volume treatise devoted to the scientific study of this substance might occasion some surprise. In fact, the general title of this work is a little misleading. While the first volume deals specifically with water itself, the remaining three promise attention to the properties of water in association with other substances, for example in crystalline hydrates, electrolyte and non-electrolyte solutions, and so on.

In 1969 Eisenberg and Kauzmann published an authoritative monograph on *The Structure and Properties of Water*, roughly half the length and a fraction of the cost of the present volume. Both books contain chapters on the properties of ice, and direct comparison shows that Franks's approach in chapter 4 of the present volume covers much the same ground, in a somewhat less detailed way, than does the corresponding chapter in the earlier book. Otherwise the organization and style of the two works are sharply contrasted. Eisenberg and Kauzmann draw on the wide range of information available in order to produce a reasonably coherent picture of the real nature of water as an isolated molecule, as a solid, and as a liquid, insofar as this is practicable with present knowledge. In this volume Dr Franks has written the chapter on ice

and an entertaining, if hardly profound, introduction on "Water, the Unique Chemical". For the rest, he has commissioned specialists to provide detailed reviews of their own fields of interest. These reviews usually include substantial sections dealing with background theoretical material, or with details of specialized experimental techniques. The task of synthesis, particularly essential when liquid water is under consideration, is, however, left to Professor Henry Frank in a concluding chapter. His literary style has echoes of Henry James, and careful reading is essential to catch the fine shades of meaning, but he sketches in admirably the subtle complexities required from any model for water which could be capable of providing a self-consistent explanation of the mass of data reviewed in the earlier chapters.

These are essentially all good, specialist, review articles. The principles of *ab initio* calculations on small molecules, and their application to the isolated water molecule, are reviewed by Kern and Karplus, while Rao summarizes calculations on the energy and geometry of hydrogen-bonded aggregates of H₂O molecules. This theoretical group is rounded-off by a discussion of the statistical mechanics of liquid water (Ben-Naim). Techniques of special importance and their application to the problem of water, particularly in the liquid state, form the second and largest group, as follows: Raman and infrared investigations (Walrafen), magnetic resonance studies (Glaser), dielectric properties (Hasted), X-ray scattering (Norton, Levy), neutron scattering (Page), acoustic properties (Davis, Jarzynski). All are detailed, informative, and express the special interests and views of their authors. A third group consists of a review of the thermodynamic and transport properties of liquid water (Kell) and one by Tödeheide on water at high temperatures and pressures. This last carries some surprises for a chemist trained to think in terms of water at atmospheric pressure and room temperature, and it is salutary to learn that hot, dense, water approximates closely to a hydroxide melt.

The material in this book is inevitably less well organized than that in Eisenberg and Kauzmann, but, in some respects, particularly in the descriptions of specialized techniques, is much more extensive; and it is more recent, an important consideration in a rapidly growing field. Faced with the moral duty of choice, one could echo Macheath's words, "How happy I could be with either". Personally, I would still buy the earlier book, and that not only for financial reasons, but make every effort to borrow this one.

H. J. V. TYRRELL

Solid Spectroscopy

Vibrational Spectroscopy of Solids. By P. M. A. Sherwood. Pp. xi+254. (Cambridge University: London, September 1972.) £5.90.

THE physics of the vibrations of crystalline solids is well developed for many simple materials. Most materials of interest to chemists, however, are powders with complex composition and structure. The interpretation of the vibrational spectra of such materials is aided by an understanding of the existing theory. This "Monograph in Physical Chemistry" is intended to present the theory of infrared and Raman spectra to final year undergraduates and research workers so that such interpretation can be attempted.

Unfortunately, in attempting to give a comprehensive account the author has left himself little room for clear emphasis of the more important aspects of the subject. Many topics are dealt with only briefly and without adequate physical interpretation. To compensate for this, supplementary material is presented in a bibliography containing nearly eight hundred references. In line with the stated aim of the book the theory presented is in general deductive rather than predictive, for example, deduction of the number and activities of vibrations by group theory is presented but the prediction of frequencies with generalized force constants or intermolecular potentials is omitted. Nowhere is there a clear statement of the chemical uses of vibrational spectroscopy. The overall effect is somewhat discouraging. Is it necessary to deal with all these complications and read all these references to understand vibrational spectra, and for what purpose?

In those areas on which some emphasis is laid the text is clear and understandable. After a brief introduction the second chapter gives a concise account of the vibrations and dispersion in one-dimensional systems. But this is followed by outlines of the problems encountered in three dimensions and in real crystals, supplemented by two hundred references. The third chapter starts with a very condensed account of group theory but compensates with a clearly worked example of the deduction of the vibrations of calcite. Further applications are again dealt with by one hundred references when the table giving some details of about fifty materials would really be ample. The ordering of the material in the next two chapters stresses the complications; generalized waves and particle shape effects are given prominence over line-width, shape and intensity. Certainly the danger inherent in the use of powders is worth emphasis, but here it is broken into two separate parts, shape effects and scattering, while

anomalies due to the Christiansen effect are omitted. The final chapter outlines other absorptions, for example magnons, which may confuse interpretation.

Overall the book is a useful reference for the research worker active in the field, but its uncritical presentation of material and references is likely to persuade others, particularly undergraduates, that there are easier fields for study.

D. BLOOR

Particle Collisions

Dissociation in Heavy Particle Collisions. By G. W. McClure and J. M. Peek. Pp. xi+198. (Wiley: New York and London, June 1972.) £5.50.

Excitation in Heavy Particle Collisions. By E. W. Thomas. Pp. xiv+436. (Wiley: New York and London, August 1972.) £9.45.

THE explosive rate of growth of research activity in many fields during the past twenty years has raised increasingly acute problems of dissemination of information. Even when the results of the research are published in the standard journals the sheer volume of publication makes it increasingly difficult to extract information in a specific field. Much of the work never gets published in this form. It remains in conference reports, preprints, or even in the notebooks of the research worker. More than twenty years ago J. D. Bernal remarked that it was becoming easier sometimes for oneself to repeat an experiment than to retrieve information about the results of earlier experiments from the literature, and since then the problem has become much more acute.

This situation has led to the growth of data compilations in various fields, continually up-dated as the results of more work becoming available, and the two books reviewed here are essentially such compilations in two rather narrow fields related to the collisions of atomic and molecular particles. Such collision processes are of great importance in many fields—gas discharge plasmas, nuclear fusion reactors, high voltage breakdown, high energy accelerators, aurorae, astrophysics, for example.

The two books have been produced as part of a project directed by the Atomic and Molecular Processes Information Centre at the Oak Ridge National Laboratory. The project itself forms part of a wider initiative of data collection being undertaken by US Government agencies associated with science and technology.

Similar compilations in the past have often been limited in their usefulness because they have been collected uncritically without much regard for the

care with which the measurements have been carried out and accepting the assessment of errors given by the authors of the papers. Indeed, with the growing emphasis on conciseness, published accounts of experiments often omit the essential detailed information necessary for an independent assessment of the significance of a particular measurement. The objectives of the present project are defined as "the collection, evaluation and critical review of data in specialized topics of heavy particle atomic and molecular collisions", and the authors seem to have given considerable attention to the critical assessment of each measurement. Where points in published work are obscure, or vital information lacking, they have written round extensively to authors. Sets of criteria have been formulated for judging the reliability of data. One feels that measurements able to pass these stringent tests can be accepted with confidence and that both books do indeed fulfil the basic aim of making reliable data available in a form useful especially for scientists and engineers who wish to use them.

These books are, however, much more than data compilations. Both contain detailed critical assessments of experimental methods written for the benefit of the specialist planning further work, and should thus be of value both for the established research worker and for research students entering the field.

The book by Drs McClure and Peek provides indexes which show where specific data on dissociation in heavy particle collisions can be found but does not actually give any data. It includes, however, a qualitative discussion of the results of experiments on the cross sections for fragmentation processes of various kinds in such collisions and on the energy and angular distributions of the fragments. It reviews the results of theoretical calculations as well as experimental measurements.

The book by Dr Thomas on excitation processes in heavy particle collisions includes for each entry in its extensive index, an assessment of the extent to which the work fails to satisfy the specific criteria formulated for judging reliability. In addition, however, it includes many tables giving cross sections for the excitation of particular states and the polarization of the subsequent radiation for processes involving excitation of both the projectile and target particles, and for excitation of the projectile following charge exchange. The data are given as a function of the projectile energy for H, H₂⁺, H₃⁺, He⁺ and heavier projectiles on targets ranging from atomic hydrogen to metallic vapours and light hydrocarbons. Data of this type on approximately 450 excitation processes are included and

the main features of each type of data are summarized critically.

In all, this represents a prodigious amount of effort and foreshadows types of presentation likely to become general for the collection of scientific information.

E. H. S. BURHOP

Photoelectron Spectroscopy

Photoelectron Spectroscopy. By A. D. Baker and D. Betteridge. Pp. x+180. (Pergamon: Oxford and New York, August 1972.) £3.50.

PHOTOELECTRON spectroscopy is a technique for studying the binding energies of electrons in the various orbitals or shells of molecules by measuring the energies they acquire when ejected by a photon of known frequency ($E_B = h\nu - \frac{1}{2}mv^2$). The subject is conveniently divided into ultraviolet and X-ray photoelectron spectroscopy, the former being concerned with the electrons in the orbitals of the valence shell and the latter with the core or inner shell electrons. The technique has proved to be far more generally applicable than conventional spectroscopic methods and in the past ten years has had remarkable success in revealing an enormous amount of detail about the electronic structure of matter.

The first book on this topic which was written by K. Siegbahn and collaborators dealt mainly with the use of soft X-rays (ca. 1,000 eV photons) to study core electron behaviour. The second book by D. W. Turner and others gave an account of the use of ultraviolet photons mainly the 58.4 nm helium line (21 eV photons) for examining the valence orbitals of molecules. The present book attempts to give an integrated account of both these aspects of the subject and to describe the main lines along which development has taken place in the last decade. It is thus a valuable introductory manual in the field, since apart from the 300 references to the more important papers on the subject it contains many tables of data which the authors have found to be of value in operating photoelectron spectrometers over a number of years. The theoretical and practical aspects of the subject are discussed with a view to showing how the results can be applied to the elucidation of organic structures, qualitative identification and quantitative analysis. The field holds great and growing interest for both chemists and physicists, and this condensed assessment of its present status is bound to be of value to them.

W. C. PRICE

CORRESPONDENCE

Six Types of Research

SIR,—Rothschild correctly points to the importance of the question, "What is the object of the classification?" but fails to recognize that different people and organizations have different needs of a classification, so that the same classification may not suit them all. Moreover, by defining strategic research as part of applied research, he makes useful analysis impossible, and he also mixes categories in his classification: classification by research type (applied, strategic or fundamental) is independent of the classification product-process-operations.

Because Rothschild refers to some of the terms we use, we would like to explain how we arrived at them. Our aim has been to classify the ARC's research in such a way that one can ask either very broad questions (for example, "What are we spending on cattle?") or much more detailed ones (for example, "What strategic reproductive physiology projects are there, related to an applied project on the improvement of techniques of artificial insemination?"). By using a matrix system and classifying each project by a number of independent categories, one can retrieve the information in many different ways, and in small or in large aggregates.

Our approach, unlike most others, has been, and continues to be, empirical. We tested our initial system on the 1,000 projects listed in our Index (*Index of Agricultural Research*, Agricultural Research Council, 1969). Our type category then contained four varieties, corresponding to applied, strategic, fundamental ("pure") and service. (The latter, not mentioned by Rothschild, covers such things as analytical or statistical services.) As we found that more than half of the ARC's work was strategic, and that it varied very much in character, some of it being closely linked with applied work and some of it not, we decided that it might prove useful to subdivide strategic research.

On the basis of experience we devised a more sophisticated classification system (*A Revised Classification System of ARC Research*, Agricultural Research Council, Planning Section Report No. 2, July 1972), again based on the matrix principle, and have used it to code all of the ARC's current 3,000 projects. Our type category now includes seven varieties. In addition to service, development, applied, and

fundamental, there are three varieties of strategic research.

(1) Strategic A: research which is required to provide understanding of a current applied project; strategic A workers either form part of the applied project team or work very closely with it.

(2) Strategic B: research carried out with the main aim of understanding some particular aspect of agriculture in order to generate specific applied projects.

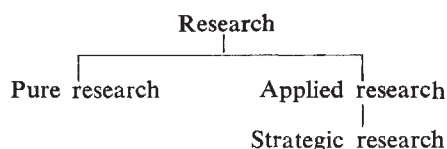
(3) Strategic C: research of an open-ended nature (with regard to application, not time as Rothschild states), but which is likely to further the scientific understanding of agriculture.

The point of subdividing in such a way is that one can aggregate as required. For example, the Parliamentary Select Committee asked the Research Councils to say what proportion of their research was spent on different types. From the definitions they gave it was possible to equate their varieties with ours, as follows:

Select Committee	ARC
Applied	Applied
Oriented—strategic	Strategic A
Basic—strategic	Strategic B and C
Basic	Fundamental

(Readers may find it instructive to compare the replies given by the various Research Councils to the Select Committee's question [*First Report from the Select Committee on Science and Technology—Research and Development*, xxxv–xlvi inc., HMSO, 237; 1972].)

Is it possible to suggest a basic classification which would be widely applicable? If one eliminates from Rothschild's Table 2 those items which logically belong to a different classification category altogether we are left with the following:



This does not seem very useful. It would be surprising if most organizations could not use five varieties as a basis: service, development, applied, strategic and fundamental. (Whether one prefers the term pure, basic, or fundamental is entirely subjective; many object to "pure", because of the

implied impurity of non-"pure" research.) Of course, some organizations may do no fundamental work, others no development, and these could then simply be omitted. Our classification has been designed with the particular needs of agricultural research in mind and not with a view to universal adoption. Each organization can subdivide any one type of research according to its own particular needs.

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Strategic Research

SIR,—Rothschild's Table 2 (*Nature*, 239, 373; 1972) may well represent the point of convergence of a protracted dispute, and certainly those who are engaged on long-range research, and yet do not object to its acquiring an ultimate application, will welcome his adoption of the term "strategic" for their activity.

It is a pity that his Glossary defines strategic research as "Research undertaken to generate specific applied programmes". Although the spirit of this seems right, the term "enable" could advantageously have been substituted for "generate", or alternatively the words "the preconditions of" inserted.

The point is not academic, as can be illustrated with the aid of a topical example. Work in a number of laboratories devoted to machine intelligence research, including that at Edinburgh, is concerned among other things with how to program computer-controlled robots to carry out tasks of assembly and/or navigation. Such studies will, without question, help to make feasible—i.e., will "enable"—NASA's "Mars Rover" project *inter alia*. However, this applied programme cannot possibly be generated by the research, but only by the skill and force of NASA's approach to Congress. Meanwhile, in case the approach succeeds, NASA has begun to create a relevant research base at the Jet Propulsion Laboratory, Pasadena. If this is to be termed "strategic" (as it surely must be) then similar research at Stanford, MIT, and Edinburgh is presumably also "strategic". The scientists concerned see it in this light and are aware that

their research will enable any Mars Rover programme that NASA or any-one else conducts.

A parallel for the creation of strategic research bases other than at the behest of a specific customer is the establishment in 1909 by the then Prime Minister, at the suggestion of R. B. (later Lord) Haldane, of the first laboratory for aeronautical research (as a section of the National Physical Laboratory).

The research initiated did not generate, but it certainly enabled, the massive aero-engineering programme subsequently forced ahead by the First World War.

Yours faithfully,

DONALD MICHIE

Department of Machine Intelligence,
University of Edinburgh

Hysteria on Hysteria?

SIR,—I am sure many of your readers are shocked and offended by your persistent efforts to heap ridicule on the Club of Rome and Professor Meadows. One cannot help but be reminded of the hysterical outbursts which greeted Malthus and Darwin. Certainly the utter limits of ridicule were reached in the alleged "comments" of the World Bank (*Nature*, **239**, 248; 1972).

The only sensible thing that can be discovered in these comments is an acknowledgment that the model of Meadows is right in its treatment of population growth.

It would surely be a waste of time and an affront to your readers to try to refute the "slashing" criticisms of the distinguished but as yet anonymous authors of this report. After all, this has already been done most thoroughly by some of the best minds in the US and elsewhere, but I cannot resist the temptation to quote the following excerpts:

Says the World Bank "report": "Meadows and his colleagues have made a patently absurd claim by ignoring the extent to which known reserves of raw materials may be still further increased by technical developments yet to come".

Say the US National Academy of Sciences and the National Research Council (*Resources and Man, a Study and Recommendations*, 1969): "All postponements allowed for, however, it is clear that exhaustion of deposits of currently commercial grade is inevitable. When the time comes for living in a society dependent on scrap and on common rock, the affluent society will be much overworked to maintain a standard of living equal to that of a century ago".

To conclude with a citation from

Professor Ravetz's *Scientific Knowledge and its Social Problems* which may not be entirely irrelevant: "The opponents of critical science will usually be bureaucratic institutions which try to remain faceless, pushing their tame experts, and hired advocates and image-projectors, into the line of battle; although occasionally a very distinguished man is exposed as more irresponsible than he would care to admit.

"In such a situation, it will not be possible for a leader of science to be both honest and tame; and if the establishment of science chooses to serve its paymasters rather than truth, it will be recognizably corrupt".

Yours faithfully,

S. V. VAECK

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Congress Caveat

SIR,—We have today received the registration form and second circular for the ninth International Congress of Biochemistry, to be held here in Stockholm on July 1–7, 1973, and would like to bring some facts to the notice of any readers who may be intending to participate in this congress. We consider that participants are being asked to pay an unrealistic sum for certain of the ancillary social events and excursions.

To quote a few examples: a steamboat trip has been organized through the Archipelago to the island of Sandhamn (conference price Sw.Kr. 75:–). However, the daily steamboat service to Sandhamn costs Sw.Kr. 24:–, excluding lunch. In addition, several companies have very cheap excursions through the Archipelago to the Finnish island of Åland. A water-bus trip around the island of Djurgården, including a visit to the 17th century ship "Wasa" will cost Sw.Kr. 27:–, while the tourist boat costs Sw.Kr. 7:–, and entrance to the "Wasa" costs Sw.Kr. 5:–. A conducted walk around the Old Town (conference price Sw.Kr. 17:–) is regularly available on Mondays and Thursdays at 7.30 p.m. for Sw.Kr. 5:–. A visit to the home and gardens of the sculptor Carl Milles (conference price, including transport, Sw.Kr. 25:–) is also available from the local bus company for Sw.Kr. 9:–. The prices quoted are valid at the time of writing.

It may also be of interest to participants to know that a month's unlimited public transport in the city and county of Stockholm is available for a present cost of Sw.Kr. 50:–. A booklet entitled *This Week in Stockholm* can also be obtained and contains full information of current tourist attractions.

We hope this information will assist participants to plan their visit to our city.

Yours faithfully,

MARIANNE ANDERSSON
TUDOR BARNARD
VIBEKE BERNSON
BARBARA CANNON
PER LUNDBERG
DAVID NICHOLLS
HEINZ NIKA
MATS OLA NILSSON
SOLVIG PALM
BERTIL PETTERSSON
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Wenner-Gren Institute,
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Repair Endonucleases

SIR,—With regard to the News and Views editorial "Mammalian DNA Repair Endonucleases?" (*Nature*, **239**, 308; 1972), we would like to draw your attention to the article we published last August (*Biochem. Biophys. Res. Commun.*, **48**, 662; 1972).

We have been in correspondence with Dr Brent and we agree that, in view of the similarity of the assay conditions and characteristics of the enzyme, we are describing the same mammalian endonucleolytic activity. Your readers might therefore be interested to know that, as we have shown, the enzyme is present in xeroderma and De Sanctis Cacchione cells and does not act at the pyrimidine dimer sites.

Yours faithfully,

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A. VAN DER PLAS
G. VELDHIJSEN

Laboratory for Molecular Genetics,
State University of Leiden, and
Medical Biological Laboratory TNO,
Rijswijk (ZH)

Caution on Creation

SIR,—I was intrigued by your news editorial "Is Continental Drift Sacrosanct?" (*Nature Physical Science*, **239**, 137; 1972), especially when compared with your previous leader "Creation in California" (*Nature*, **239**, 420; 1972). I do not endorse the method of the California State Board of Education in imposing its views; and my academic specialization does not entitle me to a free subscription to *Nature* under your dispensation to heretics—surely a happy reversal of the methods of the Inquisition! But I should like to point out the possible value of applying the argument of the first article to the subject of the second. May I quote?

"It is one of the curious paradoxes of science as a human activity that where

the larger, more important issues are concerned, dissenters from the consensus are sometimes violently reviled and sometimes praised as heroes.

"... geologists were unable to contemplate the collapse of the vast observational and intellectual edifice created by their predecessors. . . .

"But even more frightening are those people who wrote saying that continental

drift is now an accepted fact and that *Geotimes* should not print views to the contrary. . . . The history of geology is replete with long-discarded theories once regarded as well-proven facts. . . .

"But if history is anything to go by, some of the objections to drift will turn out to be insuperable and will form the seeds of an improved global model of the Earth. In the meantime, it is import-

ant that the objections are kept in view rather than swept under the carpet."

For "continental drift" read "organic evolution".

Yours faithfully,

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Obituary

Dr Harlow Shapley

WITH the passing, on October 20, 1972, of Dr Harlow Shapley less than two weeks before his 87th birthday, the world astronomical community has lost one of its outstanding leaders in the first half of the 20th century; and (by the time of his death) also one of the last survivors of its heroic age which saw the 19th century solar-system astronomy (almost) "break the barriers of the heavens"—an effort in which Shapley took a prominent part.

Born on November 2, 1885, in Nashville, Missouri, in the rural mid-west of the United States, Shapley was deflected to study astronomy almost by accident (from professional journalism), though he remained a successful writer for the rest of his life. His academic career led him through the University of Missouri (AB in 1910, AM in 1911)—where he came under the influence of Frederick H. Seares (1873–1964)—and subsequently to Princeton, then being rejuvenated under the new administration of President Woodrow Wilson, with young Henry Norris Russell (1877–1957) at the head of its astronomy department.

The time when Shapley came to Princeton could not have been more propitious. Shortly before, Russell embarked on a new approach to the analysis of the light curves of eclipsing variables in quest of the properties of the constituent stars. The arrival of a research student of Shapley's calibre was a godsend to the subject as well as to Russell himself; for thousands of observations were by 1912 awaiting analysis. Russell—aided by his never-absent slide-rule, and unimpeded by any excess of mathematical sophistication—was the guide; but without Shapley's energy in applications the new methods would not have got off the ground. Shapley's 1914 PhD thesis on the orbits of 90 eclipsing binaries virtually created in one stroke a new branch of double-star astronomy.

Having received his doctorate, Shapley joined the staff of the Mount Wilson Observatory in California. Fortune

smiled on him (and on astronomy) when George Ellery Hale (1868–1936) offered him a research post at one of the few institutions in the United States where such positions were available at that time; and Shapley made ample use of his opportunity. His scientific interests shifted from eclipsing variables—a field in which he retained lasting interest, but to which he never really returned—to globular star clusters; and with their aid he made, in 1918, what was to become his greatest single contribution to science: namely, the discovery of the dimensions of our Galaxy, and of the location of its centre.

That the distribution of such clusters in the sky is highly asymmetric (most of them are situated in one hemisphere) was known long before Shapley's time; as well as the fact that many of them contain large numbers of cepheid variables whose absolute brightness can be estimated from the periods of their light changes. Armed with this evidence, Shapley embarked on systematic study of the distribution of globular clusters in space; and found its centre to be located some 50,000 light years from us, in the direction of the galactic longitude 325° in the constellation of Sagittarius. This point Shapley boldly identified with centre of our entire Galaxy; and he was indeed right. As a result of his work, our Galaxy began to emerge for what it actually is: a stellar system at least ten times as large as all earlier estimates—from Herschel to Kapteyn—made it out to be; with our Sun located eccentrically some 15 thousand parsecs from its centre.

This latter distance was, to be sure, somewhat overestimated; for by 1918 Shapley was not yet aware of the absorption of light which a concentration of gas and dust close to the galactic plane exerts on distant objects at low galactic latitudes. The role of this "interstellar fog" did not transpire more fully until the 1930s, and it diminished our actual distance from the galactic centre from 15 to about 9 thousand parsecs; but the order of magnitude of

Shapley's earlier estimate remained unaltered.

The years 1914–1921, which Shapley spent at Mount Wilson, mark, in retrospect, the high noon of his scientific life; but Shapley did not distinguish himself only in research. Soon the world—and not only the astronomers—learned to know him as an outstanding lecturer and successful writer; in addition, Hale's example helped to develop Shapley's innate talents for administration. Small wonder that—in 1920—Shapley was offered directorship of the Harvard College Observatory, when the latter fell vacant on the death of E. C. Pickering (1846–1919). Shapley accepted; and this observatory was to remain his academic home for the rest of his life.

Under Shapley's energetic direction, the observatory's equipment was rapidly modernized, the Arequipa Southern Station transferred to become the Boyden Station in South Africa, and domestic observational activities were relegated from the proximity of the Harvard yard to the new Oak Ridge (later, Agassiz) Station some 30 miles west of Cambridge. Both the Oak Ridge and Boyden Stations were provided with new 60-inch reflectors and (in the last decade of Shapley's directorship) also with modern Schmidts. But perhaps the greatest—and certainly the most fruitful—of Shapley's innovations was the establishment of the graduate school of astronomy as a part of the educational structure of Harvard University. This school became a great success; and a list of its graduates in the 1930s reads like a *Who's Who* in astronomy today.

All these activities inevitably raised considerable demands on Shapley's time, but never made him abandon active work in galactic and extragalactic research. After he left Mount Wilson, Shapley no longer had reflectors as large as those on the West Coast within his reach. His telescopes at Harvard possessed smaller apertures, but wider angular fields. It was with these that

Shapley and his collaborators continued to explore the Magellanic clouds, to probe the spatial distribution of external galaxies; and (in 1938) discovered new dwarf galaxies in Sculptor and Fornax—discoveries which augmented the known population of the inner metagalaxy in an unexpected manner.

Then World War II came; and with it a sequence of changes the end of which is nowhere yet in sight. At its end in 1945, Shapley was 60 years of age; and as an "elder statesman" of science he was called upon to perform many extracurricular duties—such as to preside over the American Astronomical Society, the American Association for the Advancement of Science, and the National Society of Sigma Xi, almost in succession. All these duties took much of his time from the observatory and from more creative work. As a result, the last seven years of Shapley's term of office as director of the Harvard Observatory were not, perhaps, marked

by the same *élan* as the decade preceding them; and his observatory gradually yielded its leading position to others.

Shapley's retirement from directorship in 1952 (he continued to serve as research professor until 1956) brought to a close an era which kept Harvard Observatory in the forefront of astronomical progress for 75 years under the administration of two outstanding directors—a record unequalled in the annals of astronomy. Unlike his predecessor, E. C. Pickering, who died in office, Shapley survived his retirement for another 20 years; and saw the directorship of his observatory change hands no less than three times. He continued to be active as a lecturer and author for some time after 1956; but his creative powers slowly waned; and he died peacefully on October 20 of this year in Boulder, Colorado, while on a visit to his son. He is survived by his wife Martha Betz Shapley—his faithful col-

laborator already from the Princeton days, and as gracious a hostess as ever presided over the social life of any observatory, keeping her own and no small scientific abilities largely under a bushel—and five children, all of whom have been active in further development of science. Moreover, Shapley's talents as a scientist and writer are already in evidence among his grandchildren as well.

Harlow Shapley was an outstanding man of his time—astronomer, educator, author, orator, as well as man of affairs. Some of his gifts, displayed prominently in the course of his life, may gradually fall in oblivion as those of us who knew him in his prime may no longer be here to remember; and dust may settle on some of his work, or on many honours bestowed upon him by his contemporaries. But one title to fame will never tarnish—Shapley's discovery of the centre of our Galaxy, and of our position within it.

Announcements

University News

Professor G. Born has been appointed to the Sheild chair of pharmacology in the **University of Cambridge**, in succession to **Professor A. S. V. Burgen**.

Dr R. D. Guthrie, University of Sussex, has been appointed a foundation professor and chairman of the School of Science at the new **Griffith University**, Queensland.

Professor J. G. Ramsay has been appointed professor of earth sciences in the **University of Leeds**.

Dr J. R. A. Pearson, University of Cambridge, has been appointed to the chair of

chemical engineering at Imperial College, **University of London**.

Dr G. R. Dickson, principal of the Royal Agricultural College at Cirencester, has been appointed to the chair of agriculture at the **University of Newcastle upon Tyne**.

Miscellaneous

The **Tsiolkovskii gold medal** for 1972 has been awarded to **Mstislav V. Keldysh**, president of the Soviet Academy of Sciences, for his "contributions to the working out of scientific problems connected with the exploitation and use of outer space".

Dr Christian de Duve of the University of Louvain and the Rockefeller University has been awarded the **Dr H. P. Heineken-**

Prijs for 1973, for his research on lysosomes, peroxisomes and carbohydrate metabolism.

The following **Royal Society medals** have been awarded by the President and Council of the Royal Society: The Copley medal, to **Sir Nevill Mott**, University of Cambridge and Imperial College, London; The Rumford medal to **Dr B. J. Mason**, Meteorological Office; The Davy medal to **Professor A. J. Birch**, Australian National University; The Darwin medal to **Dr D. Lack**, Edward Grey Institute of Field Ornithology, Oxford; The Buchanan medal to **Sir Richard Doll**, University of Oxford; The Hughes medal to **Dr B. D. Josephson**, University of Cambridge; The Leverhulme medal to **Dr J. B. Adams**, Cern.

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